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USE OF THE VAGINAL SMEAR AS A SCREENING TEST*

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IN VIEW of the current interest in the vaginal smear and the optimistic hopes aroused by recent accounts of its usefulness, a preliminary report of a study being made by the Massachusetts Department of Public Health to evaluate the method may be helpful in clarifying its present status as a diagnostic test.

The technic for the detection of uterine cancer by means of vaginal secretions was first described by Papanicolaou[1] in 1928. In 1943 Papanicolaou and Traut[2] presented evidence of the value of this method for demonstrating carcinoma both in patients before symptoms had appeared and in those in whom clinical examination and biopsy had failed to reveal the presence of a carcinoma that was extensive enough to produce symptoms. At the same time Meigs and his co-workers[3] reported an original investigation along the same lines, with similar favorable results. In this publication the authors pointed out the possible usefulness of the smear as a routine diagnostic test and suggested that the diagnosis of vaginal smears should be available to all physicians through the Massachusetts Tumor Diagnosis Service.

In spite of general interest arising from these and a number of confirmatory reports by different workers during the past four years, the use of the method has been limited, owing in large part to difficulties of interpretation of smears and the time and training required for competence in diagnosis. The pressure of public demand resulting from recent publicity of the vaginal-smear technic has prematurely forced an answer to the question of its practicability both as a routine diagnostic method and as a screening test. The crux of the problem rests on the facts that diagnosis of smears requires wide experience and much time and that only in exceptional cases does the smear give information unobtainable by clinical examination and biopsy.

It should not be supposed that an experienced pathologist or cytologist can successfully undertake the interpretation of smears without acquaintance with the manifold variations of the structure of exfoliated cells in cases of pelvic disease and neoplasia. Accuracy of interpretation depends primarily on a familiarity with the aberrations of cells in benign and malignant states. Fortunately, a medical or scientific background is not essential for acquiring this knowledge, which may be obtained by diligence and careful observation correlated with clinical information. It will take from four months to a year to gain proficiency in this type of diagnosis, depending on aptitude and richness of material available for study.

Despite the initial difficulties and expense involved in the diagnosis of smears the method appears to be peculiarly suited for large-scale use. The limiting factor at present is the availability of technical skill. The cost per specimen varies, according to the volume, from $1.50 to $5.00. Once the necessary training has been gained, a technician can read between twenty and forty smears a day. The specimen can be obtained by relatively unskilled personnel without discomfort or inconvenience to the patient. If symptomless cancer can be demonstrated in an appreciable number of cases, the vaginal smear is an economical and practical method for use in cancer-detection clinics.

With these considerations in mind, a long-range experimental study financed by the Commonwealth Fund was inaugurated in Massachusetts in January, 1945, by the Department of Public Health to determine whether this test is of sufficient value to warrant its use in the cancer clinics either as a screening test to detect symptomless carcinoma or as a routine diagnostic measure for all gynecologic cases and, secondly, whether it should be offered

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to all physicians in Massachusetts as another form of tumor diagnostic service. An advisory committee consisting of physicians particularly interested in this diagnostic technic was appointed to assist in planning the project. This committee consisted of Dr. Thomas Almy,* Dr. John Fallon, Dr. Reginald Fitz, Dr. Joe V. Meigs, Dr. Maurice Fremont-Smith, Dr. Edward G. Huber,* Dr. Herbert L. Lombard and Dr. Shields Warren.

The following is an account of the procedure of this investigation and the initial results of two and a half years of study. Although the evaluation will not be completed for at least three years, the data at hand give some indication of what may be expected from the final analysis.

The collection and examination of the smears and the follow-up study of the patients were a joint undertaking of the Massachusetts Department of Public Health, the Tumor Diagnosis Laboratory and the state cancer clinics. All the eighteen Massachusetts cancer clinics took part in the program. Although the majority of the cases examined were from the two state cancer hospitals, Pondville Hospital and Westfield Sanatorium, several of the smaller clinics submitted smears from as high or even a higher proportion of their cases. At the time work began on this study, the vaginal smear was just beginning to be generally known, and it was therefore necessary to acquaint the staffs of the clinics with the method of obtaining secretions and preparation of the smears as well as with the purpose of the study. A prospectus of the study was sent to the physician in charge of each clinic. Personnel from the Tumor Diagnosis Laboratory studied the technic with Dr. Papanicolaou and later, on request of the chief of each clinic, gave instructions regarding the making of smears. At the end of the first six months the test had been introduced in all but three of the eighteen state cancer clinics.

The necessary paraphernalia and record forms were supplied by the Tumor Diagnosis Laboratory and the Division of Cancer and Other Chronic Diseases. Pipettes were made at the laboratory and sold at cost to the clinics. Solution bottles for fixation of smears, mailing containers and requisition cards were supplied without charge. Forms for complete data on each case were sent to the follow-up workers of the clinics, who were responsible for filling them out. Each patient examined was given a card explaining that a new test had been performed and that she would be asked to return to the clinic later. A report on each smear was sent out from the laboratory to the clinic within two or three days of receipt of the smears.

The plan of study, which is still in progress, is as follows: obtaining a single smear from each person who attended the cancer clinics between January 1, 1945, and June 30, 1947; obtaining a follow-up history and, whenever possible, a pelvic examination and a repeat smear at the end of three years after the original smear; and following for a longer period persons with unconfirmed positive smears. In a two-and-a-half-year period a single smear has been examined from each of 3586 women.

The smears were read by one technician. During the first part of the study each smear was examined for twenty minutes unless obvious carcinoma was found in a shorter time. As the number of smears increased, this rule could not be followed. No smear was examined for more than twenty minutes, but it was found that many smears could be adequately surveyed in much less time. Three forms of diagnoses were used: negative; biopsy and curettage indicated; and carcinoma, biopsy and curettage indicated. The smears with atypical, possibly malignant cells as well as many of the positive smears were reviewed by the pathologist. At the outset the pathologist and technician had had rather limited experience, but this lack was compensated for by the unfailing generosity of Dr. G. N. Papanicolaou, who gave freely of his time on several occasions and so resolved many of the difficulties that would otherwise have been a serious hindrance. Also important was the help and encouragement derived from the monthly conferences with Dr. Maurice Fremont-Smith, Mrs. Ruth Graham and their co-workers at the Vincent Memorial Laboratory, Massachusetts General Hospital. We wish also to acknowledge our indebtedness to Dr. J. V. Meigs, by whom we were first introduced to the method.

To determine how far the interest, familiarity with the method on the part of the staff of the clinics, and skill gained in diagnosis of smears would influence the study, the material is tabulated according to successive six-month periods during the two and a half years of study. The quality of the smears regarding proper spreading, fixation and so forth varied a good deal, especially in the first year. A definite improvement was seen in their preparation as time went on. Only smears that were entirely unreadable were classed as unsatisfactory. Table 1 shows a steady increase in the total number of specimens received during the first year and a half, and a gradual decrease during the second year. All the clinics alike showed the same trend.

Analysis of the records of the 3586 women examined gives the following information. There were 153 smears that were unsatisfactory for diagnosis, 434 from patients known to have a history of a uterine cancer, and 123 from patients with cancers of organs adjacent to the uterus. Among this last group positive smears might be present from extrauterine sources. Omission of these three groups leaves records of 2876 patients available for study, of whom 1364 reported symptoms suggestive of gynecologic disorders, whereas 1512 gave no his-

*Deceased.

tory of such symptoms. These 1512 symptomless patients should be representative of apparently well women so far as gynecologic conditions are concerned, and the percentage of positive smears may be considered indicative of what might be expected among such women, barring chance errors.

TABLE 1. *Participation of Different Clinics during Successive Six-Month Periods of Study.*

PERIOD	WESTFIELD	PONDVILLE	FALL RIVER	SPRINGFIELD	BOSTON DISPENSARY	LOWELL	BEVERLY	OTHERS*	TOTALS
	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	NO. OF SPECIMENS	
February–June, 1945	162	52	72	22	0	2	0	37	347
July–December, 1945	370	110	76	72	3	13	24	80	748
January–June, 1946	306	327	40	51	50	29	46	99	948
July–December, 1946	311	312	44	30	23	21	4	64	809
January–June, 1947	273	254	74	26	21	20	2	64	734
Totals	1422	1055	306	201	97	85	76	344	3586

*Including specimens from clinics that did not submit thirty smears in any of the five periods.

Eight positive smears were found, or 1 positive smear in 189 women without gynecologic symptoms. Of the 8 positive smears 5 were not confirmed by biopsy, although there is a possibility that some or even all of these patients had carcinoma in situ that will be confirmed at a later period. The true picture will probably lie somewhere between 1 in 189 and 1 in 500. Papanicolaou[4] has reported 2 symptomless cases of uterine cancer discovered by means of the vaginal smear among 500 women without gynecologic symptoms. Jones et al.[5] reported 3 cases of carcinoma discovered by the smear in patients without symptoms suggestive of carcinoma from 182 patients examined in a gynecologic endocrine clinic.

Among the 1364 persons who presented gynecologic symptoms at the time of the smear 133 positive smears were obtained — an incidence of 1:10; 89 of these positive smears were confirmed by positive biopsies, 17 had clinical diagnoses of question of carcinoma but no biopsies, and 27 furnished no evidence of uterine cancer. If only the patients with positive biopsies are considered, there would be 1 uterine cancer for every 16 women with gynecologic symptoms. The 27 smears diagnosed as positive but unconfirmed from the group of 1364 women with gynecologic symptoms combined with the 5 positive smears from those without a history or symptoms of gynecologic disorders make a total of 32 persons showing positive smears with no apparent uterine cancer at the time of the original smear.

A more detailed account of the smear diagnoses is presented in Table 2. The classifications are based on the diagnoses made on biopsy either at the time of smear or within a few days. On follow-up study it is probable that the classifications will be altered. The time required for final evaluation of a case will vary from a few days to three years. For example, a positive biopsy would confirm a positive smear, but in cases of carcinoma in situ, some time might elapse before a positive biopsy could be obtained to confirm a positive smear. Persons with negative smears, regardless of whether or not symptoms are present, are to be followed for

TABLE 2. *Preliminary Results of the Cytologic Test for Uterine Cancer (January 1, 1945, to July 1, 1947).**

EVALUATION OF CASE	POSITIVE SMEARS†		QUESTIONABLE SMEARS		NEGATIVE SMEARS		TOTALS	
	NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE		
No history or symptoms of gynecologic disorder:								
Evidence of uterine cancer (positive biopsy at time of smear)	3	75.0	1	25.0	0	—	4	
No evidence of uterine cancer	5	0.3	49	3.3	1454	96.4	1508	
Totals	8		50		1454		1512	
Symptoms of gynecologic disorder but no known uterine cancer:								
Evidence of uterine cancer (positive biopsy at time of smear)	89	59.3	39	26.0	22	14.7	150	
Evidence of uterine cancer (clinical diagnosis at time of smear)	17	50.0	7	20.6	10	29.4	34	
No evidence of uterine cancer	27	2.3	104	8.8	1049	88.9	1180	
Totals	133		150		1081		1364	
Grand total								2876

*Of the total of 3586 records collected 2876 were used, the remainder consisting of 434 specimens from patients with a history of uterine cancer, 153 specimens that were unsatisfactory and 123 specimens from patients with cancer of organs adjacent to the uterus, which might have given false-positive smears.

†The proportions of positive smears were 1:189 in the total 1512 patients with no history or symptoms of gynecologic disorders (1:504 in the group in which the diagnosis was confirmed by biopsy) and 1:103 in the total 1364 patients with symptoms of gynecologic disorders (1:15.3 in the group in which the diagnosis was confirmed by biopsy). Many of these percentages are based on too small numbers to be significant.

three years. Those with positive smears, not confirmed by biopsy, are to be followed for a longer period.

The accuracy of the test depends on two factors, both of which elude strict analysis: the adequacy of the smear in representing the state of the genital tract, and the accuracy of interpretation of cells. The representative character of the smear has been found by different observers to be reliable in from 80 to 94 per cent of cases.[6] The wide range of these findings probably depends on whether a single examination or multiple examinations were used for judging the accuracy of the smear method in the individual case. The over-all error of interpretation has been reported as between 0.3 and 4.0 per cent in large series of cases (Table 3).

TABLE 3. *Comparison of Results in Large Series of Cases Examined by Vaginal Smear.*

SOURCE	NO. OF CASES	NO. OF SMEARS	PROVED CASES OF CANCER	FALSE-POSITIVE DIAGNOSIS		FALSE-NEGATIVE DIAGNOSIS		TOTAL ERROR	
				CASES	SMEARS %	CASES	SMEARS %	CASES	SMEARS %
Papanicolaou and Traut[2] (random cases)	3,014	7,000 10,000	194	—	—	11	6.0	11	0.3
Meigs et al.[3]	1,015	1,559	154	25	2.9	16	10.3	41	4.0
Gates and Warren[4]	1,300	1,300	81	16	1.3	19	23.0	33	2.5

The method of computation of the percentage of error in general use has been to divide the number of mistakes by the total number of positive or negative cases to determine the false-positive or false-negative error. For example, in Table 3 the 23.0 per cent false-negative smears means that among known cancer cases the smear diagnosis was correct in 77 and wrong in 23 per cent. It would probably be better to substitute for "false negative" the words "errors in diagnosis among cancer cases," since the present terminology is confusing and may give an erroneous impression. Examination of the data in Table 3, in which the results for the first thirteen months of this study are presented along with the large series reported by Papanicolaou and Traut[2] and by Meigs et al.,[3] suggests that the false-negative diagnosis, or error among cases of cancer, is from five to twenty times more frequent than the false-positive diagnosis, or error among patients without cancer.

The smears that were misinterpreted have been reviewed, and almost without exception the error was at once obvious. It is undoubtedly true that false-positive diagnoses may be avoided provided that only the smear with typical numerous tumor cells is accepted as evidence of carcinoma. If this rule is followed, a positive diagnosis will not often be made, and one must rely on suggestive or descriptive reports.

In this study smears that showed atypical but not distinctly malignant cells were reported under the heading of biopsy and curettage indicated. The smears in this category, 261 in number, included those in which the evidence of a few cells was strongly in favor of carcinoma, and those in which the atypical forms present were not definitely suggestive of cancer but were yet unaccountable. This is the most interesting group of the whole series inasmuch as early and premalignant lesions might be expected here if anywhere. The answer to the question of the practicability of the vaginal smear as a screening test may be decided by the evidence that the follow-up on these cases will bring forward.

TABLE 4. *The Vaginal Smear as an Ancillary Method for the Demonstration of Early and Obscure Cases of Carcinoma.**

SOURCE	TOTAL CASES	CANCER OF UTERUS	SYMPTOMLESS CASES	POSITIVE SMEAR WITH NEGATIVE BIOPSY	EARLY CANCER OTHER THAN CANCER IN SITU	CANCER IN SITU
Papanicolaou and Traut[2]	3,014	180	2	3	9	7
Meigs et al.[3, 7]	1,015	148	—	—	16	3
Papanicolaou[5]	500	2	2	—	—	—
Jones et al.[†]	182	3	3	—	—	—
Gates and Warren[4]	1,554	142	1	2	2	1
Totals	6,265	475	8	5	27	11

*The total number of cases in which the vaginal smear was of special value cannot be determined inasmuch as it is not certain from the reports which cases were placed in more than one of the categories listed.

†These figures do not represent the total cases reported by these authors but only the group among which the unsuspected cases were found.

DISCUSSION

There is no indication for using the vaginal smear as an adjunct to biopsy in the ordinary case of pelvic disease, and the application of the method

as a screening test, although more economical than other procedures available for detection of the earliest stages of cancer among large groups of apparently well persons, is not likely to bring to light many cases.

The rather startling results obtained by the use of the vaginal smear in certain cases must be considered in relation to other factors such as the proved efficiency of the biopsy in disclosing early lesions and the possibility of curing lesions that, though still early, have given rise to symptoms. The early carcinomas with symptoms far outnumber the symptomless cases discovered (Table 4). Among 6265 patients examined by the vaginal smear only 8 symptomless carcinomas were found, but there were an estimated 39 "early" carcinomas that produced symptoms and were diagnosed by a positive biopsy as well as a positive smear. In only 5 cases of carcinoma was the initial biopsy negative while the smear was positive. The recent reports of carcinoma in situ by Fremont-Smith et al.[8] and Isbell and his co-workers[9] indicate that most cases of carcinoma in situ present symptoms, although they are not always recognized as suggestive of cancer.

One of the important things the vaginal-smear technic has done has been to enlarge our understanding of symptoms and signs that should be considered as possible evidence of early carcinoma. It is not, we believe, generally appreciated what an impetus to the interest in early carcinoma has resulted from the studies on the application of the vaginal smear carried out by Dr. Papanicolaou, Dr. Meigs, Dr. Fremont-Smith and their associates. In broadening the concept of the medical profession regarding early manifestations of carcinoma, these workers have performed an unusual service in the field of education.

The technic is more likely to lower cancer mortality because it has made a large number of physicians aware of the insignificance of the signs and symptoms that may be associated with early carcinoma of the uterus than because of the number of early cases it discloses.

Summary

The present findings indicate that by the cytologic test for cancer it may be possible to find 1 case of uterine cancer among 200 to 500 women free from symptoms. The final evaluation of the technic as a screening test cannot be made until the results of the follow-up study are known three years hence.

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SEVERE HYPERTENSION WITH PAPILLEDEMA SIMULATING BRAIN TUMOR*

Differential Diagnosis and Treatment

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ESSENTIAL hypertension is a very common condition, and expanding intracranial lesions are common enough so that coexistence of the two may be anticipated. The symptoms (impairment of vision, headache, nausea, vomiting, convulsions, stupor, unconsciousness and coma), physical findings (papilledema and localizing signs) and spinal-fluid alterations (increased pressure and elevated protein) may occur both in severe hypertension and in brain tumor. Increased intracranial pressure associated with a slowly expanding intracranial lesion is not accompanied by a significant increase in the blood pressure. The presence of an acutely expanding intracranial lesion (from trauma or hemorrhage), which may cause an elevation of the blood pressure, is usually apparent. The differential diagnosis, therefore, is not a mutually exclusive one. The choice is between the severe form of hypertension with papilledema (Grade IV or malignant hypertension) and brain tumor with coexisting hypertension. Actually, in our experience the presence of brain tumor often requires consideration in patients with severe hypertension. Sometimes the suspicion of brain tumor remains in such patients, the possibility persisting in spite of appropriate and detailed investigation. Rarely, brain tumor in association with hypertension has mistakenly been considered severe hypertension with papilledema, and conversely exploratory craniotomy has sometimes been performed because an expanding intracranial lesion could not be excluded positively.

Because of the similarity in symptoms and signs between these two conditions and because patients have been encountered in whom essential hypertension and brain tumor coexisted, we have compared the symptoms, signs and spinal-fluid findings in 30 patients with severe hypertension and papilledema, in 25 patients with proved brain tumor and in 15 patients with severe hypertension but without papilledema. We wish to clarify this important problem.

DIFFERENTIAL DIAGNOSIS

From a review of our data, striking similarities are apparent. In differentiating severe hypertension with papilledema and expanding intracranial lesions with coexisting hypertension, the following observations are pertinent.

Severe hypertension with papilledema (Grade IV or "malignant") is most frequent under the age of fifty. Brain tumor is widely distributed at all ages. Severe hypertension without papilledema (Grade III) occurs most frequently at middle life and after, and is a little more common in women than in men. Grade IV or malignant hypertension is more common in men.

Headache appears to be actually more frequent and possibly more severe in the hypertensive cases. Symptoms referable to the heart are naturally more common in patients with hypertension, but would be expected equally in patients with brain tumor and coexisting hypertension. Cerebrovascular accidents are likely to be sudden and progress rapidly either toward improvement or to death, whereas the neurologic changes associated with brain tumor are more likely to be slowly and steadily progressive with or without episodic exacerbations. (*This difference in the course of the symptoms is, as a rule, one of the most important differential points.*) Our patients with hypertension and papilledema were taken for study as they appeared and were not selected because of hypertensive crises or hypertensive encephalopathy. It so happens that only 1 of this series of 30 patients had convulsions and unconsciousness. When hypertensive encephalopathy occurs there may be coma or stupor, with or without convulsions that may be general or unilateral, and with or without paresis. These crises may result in death or in recovery without residual symptoms. In brain tumor the neurologic changes are persistent and progressive. In the 25 patients with brain tumor convulsions occurred in 9, and unconsciousness in 12.

In the appearance of the fundi the character and degree of papilledema, the presence of atrophy and the finding of hemorrhages are not positively differential (Table 1). In one patient with brain tumor and without coexisting hypertension, exudate was found by a competent ophthalmologist. On the other hand, papilledema alone without hemorrhage or exudate occurred in 4 of the patients with hypertension. Unilateral choking with optic atrophy on the opposite side was found in 1 case of malignant hypertension, brain tumor being excluded by autopsy.

Of the 10 patients with hypertension and choked disks, the elevation was recorded as "several diop-

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ters" in 3, four diopters in 1, three diopters in 2, two diopters in 1, one or two diopters in 1, and one diopter in 2. Of the eleven patients with brain tumor and choked disk, the elevation was four diopters in 4, three diopters in 2, two diopters in 2, and one diopter in 3.

Marked vasoconstriction is the prime characteristic of hypertension with papilledema and might be a differential point except that it may also occur with incidental hypertension in patients who have brain tumor. Judgment of the degree of arteriolar constriction may be an important factor, since ordinarily the most marked degree of vasoconstriction is found in severe hypertension with neuroretinitis.

The findings from lumbar puncture offer guidance but not positive differentiation (Table 2). Increased spinal-fluid pressure may occur in severe hypertension either with or without papilledema. The maximum elevation of cerebrospinal-fluid pressure (500 to 700 mm. of water) occurred in the patients with brain tumor. In the patients with malignant hypertension and papilledema the pressure never exceeded 450 mm. of water. It is evident that elevation of the cerebrospinal-fluid pressure is not a differential criterion. The same statement may be made of the spinal-fluid protein, though from a comparison of these three groups of patients, the higher the spinal-fluid protein the more likely is brain tumor (Table 3). The patients with hypertension may have a high protein, but it is more likely to be normal than that in patients with brain tumor. A slightly elevated protein is occasionally encountered in severe hypertension without papilledema. In only 2 of the patients with hypertension and choked disk (more than one diopter) was the nonprotein nitrogen over 40 mg. per 100 cc. initially. In several cases the nonprotein nitrogen rose terminally. As for the goldsol curve, rises in the midzone were quite common both in patients with brain tumor and in those with severe hypertension and papilledema, whereas in patients with severe hypertension without papilledema slight alterations in the midzone occurred but were less notable.

One is forced to the conclusion that an intracranial tumor often must be ruled out when severe hypertension with papilledema (Grade IV, "malignant" hypertension) is encountered and that data from lumbar puncture alone, although helpful, are not positively diagnostic. Since coincidence of hypertension and brain tumor may be anticipated statistically, it will be dangerous to ascribe to hypertension abnormalities in fundi or in the cerebrospinal fluid that could be caused by brain tumor. Study is not complete without a competent neurologic examination, skull plates, an electroencephalogram and sometimes air-injection studies.

TABLE 1. *Examination of the Fundi.*

DIAGNOSIS	NO. OF CASES	CASES WITH NO EDEMA OF DISKS	CASES WITH PAPILLEDEMA*	CASES WITH CHOKED DISK†	CASES WITH HEMORRHAGE	CASES WITH EXUDATE
Grade IV (malignant or severe hypertension with papilledema)	30	0	20	10	24	26
Brain tumor	25	8	6	11	6	1
Grade III (severe hypertension without papilledema)	15	15	0	0	3	6

*Less than 1 diopter.
†1 diopter or more.

TABLE 2. *Spinal-Fluid Examination.*

DIAGNOSIS	NO. OF CASES	INITIAL PRESSURE		
		300 or more	*200–299*	*199 or less*
Grade IV (malignant or severe hypertension with papilledema)	30	11	14	5
Brain tumor	25	18	3	4
Grade III (severe hypertension without papilledema)	15	2	5	8

TABLE 3. *Total Protein on Spinal-Fluid Examination.*

DIAGNOSIS	TOTAL PROTEIN			
	100 mg./100 cc. or more	*75 to 99 mg./100 cc.*	*50 to 74 mg./100 cc.*	*49 mg./100 cc. or less*
Grade IV (malignant or severe hypertension with papilledema)	3	4	7	16
Brain tumor	8	7	3	7
Grade III (severe hypertension without papilledema)	1	2	2	10

CASE REPORTS

CASE 1. In 1935 a 57-year-old woman entered the hospital with a history of known hypertension and exertional angina pectoris of 10 years' duration. Failing memory had been noted for 5 months, and she had complained of severe frontal and left-sided headaches and had been stuporous for 9 days. For the 12 hours prior to entry there had been vomiting and coma. The blood pressure at entry was 180/100. Examination

of the fundi showed papilledema of 3 or 4 diopters bilaterally, narrowing and tortuosity of the arterioles, hemorrhages but no exudate. There were no localizing neurologic signs, though the family thought the patient's actions had been peculiar, talk had been senseless, and there may have been drooping of the left eyelid. No difference in the size of the pupils was noted. An attack of severe substernal pain had occurred on the day of admission. Lumbar puncture showed an initial pressure equivalent to 350 mm. of water and a total protein of 34 mg. per 100 cc. The nonprotein nitrogen was 41 mg. per 100 cc. The diagnoses were severe hypertension, with hypertensive encephalopathy and neuroretinitis, and hypertensive and arteriosclerotic heart disease with angina pectoris. Lumbar puncture was performed twice, with apparent improvement in the clinical condition. In the course of a few days rales appeared at the bases. The temperature rose to 104°F.; the patient died. At autopsy an unsuspected glioblastoma multiforme in the left frontal lobe was found, with signs of increased intracranial pressure (flattening of the convolutions), wet lungs, a slightly enlarged heart and coronary sclerosis with healed myocardial infarction.

This patient was rather old to be typical of severe hypertension with neuroretinitis. Her blood pressure, especially the diastolic, was too low to be typical. Concentration on the obvious and severe vascular disease, including disease of the retinal arterioles and the hypertension, and failure to evaluate properly the history and clinical findings misled the observers in this case. Known antecedent severe vascular disease and the recent cerebral symptoms were wrongly taken to be cause and effect. Lumbar puncture was a hazardous and ill considered procedure. This maneuver should not be done in patients with increased intracranial pressure before the needed information to be obtained has been balanced against the risk of inducing a pressure cone.

CASE 2. A 63-year-old housewife had had variable hypertension for 1 year and 7 months and complained of unsteadiness and of soreness in the neck since a fall 6 months before admission. She stated that her eyes did not respond to her wishes. She was troubled by weakness of the arms and finally by numbness of the right side of the face and tongue with increasing deafness and tinnitus on the right. Blurring of the optic disks was found. Her blood pressure was as high as 200/125 when she was ambulatory and as low as 130/78 at rest. Lumbar puncture revealed an initial pressure equivalent to 150 mm. of water, a total protein of 80 mg. per 100 cc. and a negative spinal-fluid Wassermann test. On exploratory craniotomy an acoustic neuroma in the right cerebellar pontine angle was found and removed. A year later she was known to be alive though still having some difficulty in walking.

The variable though at times very high blood pressure was incidental to the brain tumor, which, in this case, was obvious from the typical history of steadily progressive neurologic change.

CASE 3. A 45-year-old woman had had hypertension (a blood pressure of 190/130) for 1 year and 3 months and constant headaches of 10 years' duration. On entry to the hospital in 1938 she complained of poor vision in the left eye and intermittent diplopia of 9 months' duration. A few days before admission there had been transient numbness of the lower lip and tongue and left lower arm. Her father and one brother had died suddenly at 65 and 47 years of age respectively. Bilateral choked disks were found (4 diopters on the left and 1 diopter on the right). The retinal arterioles were markedly attenuated. There were no exudates or hemorrhages. Examination of the urine was negative. Renal function was normal. On lumbar puncture the initial pressure was equivalent to 330 mm. of water The spinal-fluid protein was 29 mg. per 100 cc. The spinal-fluid Wassermann reaction was negative, as were blood Wassermann and Hinton tests. X-ray films of the skull showed a grossly abnormal sella. A ventriculogram demonstrated both lateral and third ventricles to be displaced to the right. A left temporoparietal craniotomy revealed the brain under moderately increased pressure. The tumor proved to be an aneurysm of the internal carotid artery. Nothing could be done, and the wound was closed.

The gradually enlarging aneurysm in this case may have been primarily responsible for the recent symptoms and the increased intracranial pressure. Nevertheless, it was not possible to exclude with certainty the severe form of hypertension with papilledema. In support of this diagnosis were the headaches and poor vision since the age of thirteen, a known duration of hypertension of one year and three months with a very high diastolic pressure, marked attenuation of the fundus arterioles and age well within the usual range of severe hypertension with papilledema. In favor of a slowly developing intracranial tumor were the constant left-sided headache for several years, progressive failure of vision more marked on the left for several weeks, deformity of the sella and displacement of the lateral and third ventricles to the right.

With the recent increase in interest in and knowledge of intracranial aneurysm the disturbances in ocular movement and trigeminal hypesthesia, together with deformity of the sella, should have suggested the correct diagnosis. Precise interpretation is difficult, but we suspect that this patient may be an example of the coexistence of the severe form of hypertension with papilledema and an expanding intracranial lesion. It is reasonable to suppose that the very severe hypertension hastened the expansion of the aneurysm of the internal carotid artery.

Other observers have found this differential diagnosis interesting and at times difficult, as Cushing and Bordley[1] did forty years ago. Abbott et al.[2] report the case of a female patient aged forty-eight, who had hypertension and complained of weakness of the left hand for several years and who for two years had experienced convulsive seizures with residual paresis of the left arm and leg. In this case there was no papilledema, but the persistent localizing signs and the seizures should have suggested neoplasm with coexisting hypertension. Nevertheless, the patient was treated for the hypertension for over a year. The treatment included bilateral partial adrenalectomy after which there was apparent improvement in the blood-pressure level. Continued convulsive seizures and the persistent localizing signs finally led to skull plates, which showed bony change in the central region. At craniotomy a 150-gm. meningioma was removed.

Grant[3] reports 5 cases seen in the course of two years diagnosed as suspected brain tumor because of choked disks, headache and suggestive neurologic signs. Before renal vascular disease was conclusively demonstrated, the neurologic symptoms and

evidence of intracranial pressure appeared positive enough to warrant exploration. Craniotomy was done in 2 cases, and the author refers to similar experiences of others. The French school stress this similarity between severe hypertension with papilledema and space-taking intracranial lesions by referring to it as pseudotumoral hypertension.[4-8] From the cases cited the need for combined medical and neurologic study of these problems is obvious. With increasing use of air studies in the preoperative workup of cases in which brain tumor is suspected, which today is the custom in most clinics, errors of the sort reported are not likely to occur. We believe that this procedure should be routine in doubtful cases, especially when convulsive seizures or localizing neurologic signs are present.

Prognosis, Mortality and Efficacy of Sympathectomy

The outcome in these 30 cases of the severe form of hypertension justifies the ominous significance usually ascribed to the combination of hypertension and papilledema. The status of 2 patients is not known. Of the remaining 28 patients 3 are known to be alive nine to ten years after hospital study. Of the others 1 survived seven years, and 5 others survived between one and two years after hospital observation. The rest were dead in less than a year.

Four were postoperative deaths: 3 after dorsal sympathectomy and 1 after right nephrectomy for pyonephrosis, actually from bilateral adrenal hemorrhage. Three patients died with cerebral accidents. Congestive heart failure was the chief cause of death in 1 case, a contributory cause of death with uremia in 2 and was associated with cerebral accident in another. Uremia was a cause of death in 8 patients. One patient with adrenal paraganglioma died in a paroxysm of hypertension. One died a respiratory death, evidently from a pressure cone; spinal puncture had not been done within two months. Seven patients died away from the hospital, the precise cause being undetermined.

Nine of the patients who died were autopsied, and in 7 of these the brain was examined. Aside from varying degrees of arterial and arteriolar disease, hemorrhage was present in 1 case, infarction in 3, a definite pressure cone in 2 and a questionable pressure cone in a third. In 1 the ventricles of the brain were enlarged to one and a half times their normal size. Hypertrophy of the heart was found in 8 cases, but the heart of the patient who died in a paroxysm of hypertension due to a paraganglioma was not enlarged. Malignant vascular nephritis was diagnosed pathologically in 3 cases and was questioned in 1. Chronic vascular nephritis was diagnosed in 3 cases. Only slight intimal thickening of the renal arterioles was found in the remaining kidney of the patient who died after nephrectomy. The kidneys of the patient with the adrenal paraganglioma were normal.

In this series of 30 patients with hypertension and papilledema, dorsal sympathectomy was performed in 15, and dorsolumbar sympathectomy in 1. Two of these died soon after operation. These deaths were ascribed to the advanced stage of the disease when the patients were operated upon. The third operative death was due to bilateral pneumothorax. Of the remaining 12 in whom dorsal sympathectomy was performed, 6 patients died within a year, and 3 within two years. One survived seven years after operation. Two patients are living ten years after dorsal sympathectomy. In 1 of these the blood pressure was unchanged, but the papilledema of two or three diopters entirely cleared up. In the other, eye grounds and vision became almost normal, but extensive peripheral vascular disease had developed. Another patient, one of the first to have dorsolumbar sympathectomy, is alive nine years after operation, but her precise condition is unknown.

Discussion

Is papilledema of whatever degree, even though of less than measurable elevation, an infallible sign of the severe rapidly progressive form of hypertension? The uniformly fatal outcome in this group, except for 4 cases in which sympathectomy was performed, whether the papilledema was more or less than one diopter, certainly suggests that these patients have something in common that is of ominous significance. The foremost sign of this, we believe, is edema of the optic disks. When we refer to malignant hypertension clinically, we mean the patients usually under fifty years of age who, with or without a previous known hypertension of milder degree, present severe symptoms of recent onset, commonly with intractable headache and failure of vision, who have a very high diastolic blood pressure and papilledema, and most of whom pursue a rapidly progressive clinical course to death within two years. This does not mean that in every case a pathological diagnosis of malignant nephrosclerosis (necrotizing arteriolitis) will be made at autopsy.

The possibility remains that all the patients with the diagnosis of malignant hypertension do not necessarily have an extremely poor prognosis. Mistakes may be made in patients with severe arteriolar sclerosis with extensive hemorrhages and exudate and in certain patients with marked vasospasm when the accompanying edema may not be so serious. In 1 of the patients surviving ten years after dorsal sympathectomy the presence of pathologic blurring or edema of the disks was somewhat questionable and, if present, may have been due to extensive vasoconstriction, hemorrhages and exudates. The acute onset, severity and apparent rapid progression of his disease indicated malignant hypertension. Individual cases of remission[9] and even prolonged survival[1,0] after a clinical diagnosis of malignant hypertension are on record, but these are considered exceedingly rare. The correctness

of diagnosis and prognosis is indicated by the fatal outcome in 90 per cent of cases so diagnosed in two years. The efficacy of sympathectomy may be judged by the survival time of patients in whom malignant hypertension was diagnosed clinically who have been sympathectomized, as compared with those not so treated.

Keith, Wagener and Barker[11] reported 146 cases of malignant or Grade VI hypertension, of whom 79 per cent were dead in one year, 88 per cent in two years, 94 per cent in three years, 98 per cent in four years, and 99 per cent in five years. Our experience to date with the medical management of malignant hypertension is in accord.[12] The survival for seven to ten years of 3 out of 15 of our patients in whom dorsal sympathectomy was performed has been noted. Peet and Isberg[13] reported 21 patients (19 per cent) of 112 with malignant hypertension alive five to eleven years after dorsal sympathectomy. It was noted above that 1 of the first patients to have dorsolumbar sympathectomy is living nine years after operation, and it has been reported elsewhere that 5 of 11 patients with malignant hypertension were living three to five years after dorsolumbar sympathectomy.[14] Hammarström,[15] in reporting his experience with 101 hypertensive patients sympathectomized in the past five and a half years, states that of 17 patients with malignant hypertension sympathectomized, the median and mean length of life is definitely greater that that in the control material of Keith and Wagener.[9]

It is admitted that an exceptional case in which sympathectomy was performed may have erroneously been diagnosed as malignant hypertension, and that the patient may therefore have survived longer. It is also possible that the severity of the disease varies in patients who exhibit the clinical features of malignant hypertension, those with less severe disease surviving longer whether or not sympathectomized. Nevertheless, the mortality bears out the diagnosis and prognosis uniformly in the unoperated cases, and the operated cases exhibit the same clinical features. The important fact is that these clinical features are changed in a number of the operated patients. When successful, operation relieves the intractable headache, the papilledema disappears, and the rapid, intense course of the disease is slowed.

That the changes in advanced malignant hypertension may be reversed by sympathectomy is illustrated by the following case report.

A 35-year-old Navy officer, who had been working in the Radiation Laboratory at Massachusetts Institute of Technology, had complained of unusual fatigue for 6 months and headaches for 3 months, followed by blurring of vision and nocturia of 1 month's duration. Ten days prior to admission to the United States Naval Hospital in Chelsea he had suffered a series of convulsions, with amnesia, and had fallen out of bed injuring his forehead. On May 31, 1943, his fundi showed severe papilledema (5 diopters), with much exudate and scars of old hemorrhage. His heart was of normal size, but an electrocardiogram showed hypertensive changes. Neurologic examination was negative. The urine gave a + test for albumin and contained a maximal concentration to a specific gravity of 1.021; the nonprotein nitrogen was 34.5 mg. per 100 cc. An intravenous pyelogram was normal, and phenolsulfonephthalein excretion was satisfactory. Events are best recorded in chronologic order, as follows:

On May 19 the patient had convulsions. The cerebrospinal-fluid pressure was equivalent to 390 mm. of water, and the protein was 20 mg. per 100 cc.

Two days later the blood-pressure readings were 200/130 (recumbent), 190/140 (sitting) and 200/150 (standing). When the arm was immersed in ice water the blood pressure rose to 300/180.

On June 4, when the patient had had recurrent convulsions for the past 2 days, the fundi showed many recent hemorrhages.

On June 7, thoracolumbar sympathectomy (ninth thoracic to first lumbar segment) was performed by one of us (J.C.W.).

On June 15 the patient complained of more blurring of vision. Vertigo and headache were so intense that he could not get up. The blood pressure was 200/120.

On June 22 left thoracolumbar sympathectomy (eighth thoracic to second lumbar segment) was performed by one of us (J.C.W.). The blood pressure fell to 78/40.

On July 2 the blood pressure was 150/90. The patient noted improvement of vision. His headaches had disappeared, and he was no longer dizzy. He was out of bed and comfortable.

On July 8 the blood-pressure readings were 146/90 (recumbent), 136/90 (sitting) and 130/80 (standing). The cerebrospinal-fluid pressure was equivalent to 220 mm. of water.

On August 14 there was remarkable improvement. The patient felt well and was swimming and skipping rope. He was discharged from the hospital on sick leave.

On December 21 the papilledema was gone, and the retinal exudates and hemorrhages had cleared. Vision had returned to normal, but the patient still tired easily and complained of occasional headaches. He had returned to work, and gave the interesting story of how, prior to his cerebral crisis, he had been working on an important problem in radar electronics. He had entirely lost track of this work, but after returning to his desk had soon picked up these ideas from his previous notes.

On August 1, 1944, he was working hard but tired easily. The blood pressure was 168/118; the heart was not enlarged. The urine was normal and the nonprotein nitrogen was 36 mg. per 100 cc. The fundi were normal except for narrowed arteries with arteriovenous nicking.

On May 6, 1947 (4 years after sympathectomy), the patient was reviewed by Dr. K. A. Evelyn at the Hypertension Laboratory of the Massachusetts General Hospital. He was then an insurance salesman and doing regular work with only the complaints of slight fatigability and occasional mild headaches. Examination of the fundi revealed normal disks and a few residual scars of the old hemorrhages. There were moderate changes in the caliber of the retinal arteries, slight arteriovenous compression and barely noticeable broadening of the light reflex. An electrocardiogram showed only minimal hypertensive changes. The blood-pressure readings were 170/120 (recumbent) 160/110 (sitting) and 150/115 (standing). The rise on cold-pressor test was to 200/140 as against the preoperative rise to 300/180.

It is evident that the severe cerebral and retinal changes in this case of malignant hypertension were reversed and have remained controlled for four years. Although the patient has had a partial re-elevation of blood pressure to a more moderate hypertensive level and has mild residual symptoms, he has been able to lead a moderately active life and to earn his living.

Direct surgical relief of the hypertensive syndrome of increased intracranial pressure by decompression was suggested by Cushing and Bordley[1] in 1908. Grant[2] performed cerebral decompression in 2 patients and referred to similar experiences of others. Shelburne, Blaine and O'Hare[16] suggested

that in certain selected cases, in the hands of a competent surgeon, cerebral decompression may be justified in the presence of advanced visual failure. Dereux[17] advocates this procedure in the face of positive evidence of increased cerebrospinal-fluid pressure, progressive symptoms and ineffectiveness of medical measures.

On review of our own experience in the treatment of the hypertensive syndrome of increased intracranial pressure, both medical and surgical, and some of the reported surgical experiences of others, we conclude that cerebral decompression alone is rarely justified. Our reasons are as follows:

Craniotomy is a radical and dangerous procedure that by itself as a rule offers only doubtful and temporary relief in the rapidly progressive course of an almost always rapidly fatal disease.

Venesection, drainage of the spinal fluid by lumbar puncture (with caution and only when an intracranial neoplasm has been excluded), hypertonic intravenous infusions and free use of intramuscular or intravenous magnesium sulfate are as often followed by as much relief, or recovery occurs spontaneously.

If improvement does not follow medical treatment, we think that irreversible pathologic change, thrombosis with infarction or hemorrhage of greater or lesser degree — or a combination of all three — is very likely. Craniotomy in this situation in the present state of knowledge and technic is not justified.

Kempner[18] has reported 33 patients "with papilledema, hemorrhage or exudate" who followed the rice diet for a period of at least eight weeks. In 21 cases "the retinopathy improved greatly or even cleared up entirely under the rice regime." The retinal photographs taken before and after treatment leave no doubt about the extraordinary improvement. The Selyes[19] are encouraged by the favorable results in malignant hypertension that follow the long-continued use of a low-sodium, low-protein, low-fat diet with high carbohydrate and large doses of ammonium chloride. Our experience with these regimes is not yet extensive enough for us to comment authoritatively. To date, the only patients with severe hypertension and papilledema whom we have seen definitely helped for considerable periods have been those submitted to sympathectomy. Final judgment of efficacy between the various surgical technics and medical regimes will depend upon the survival time of patients who conform to the clinical criteria for the diagnosis of malignant or Grade IV hypertension.

Summary

The similarity in symptoms, physical signs and spinal-fluid findings between severe hypertension with papilledema and expanding intracranial lesions is pointed out. A comparison is made of observations in 30 patients with severe hypertension and papilledema, in 25 patients with expanding intracranial lesions and in 15 patients with severe hypertension without papilledema.

The differential diagnosis between severe hypertension with papilledema and an expanding intracranial lesion with coincident hypertension is discussed and illustrated by a report of 3 cases. The most important differential characteristic is the slow, steady progression of neurologic localizing signs in brain tumor. Proper evaluation depends upon expert neurologic examination and sometimes upon supplementary pneumograms.

In our hands extensive sympathectomy has thus far been the measure that has relieved symptoms, reduced the papilledema and stayed the rapid progress to a fatal outcome that is almost uniform in patients with malignant hypertension. It is suggested that denervation of the splanchnic bed abolishes or minimizes the orthostatic pressor responses and thus protects the cerebral circulation.

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EFFECTIVENESS OF VITAMIN B_{12} IN COMBINED SYSTEM DISEASE*

Rapid Regression of Neurologic Manifestations and Absence of Allergic Reactions in a Patient Sensitive to Injectable Liver Extracts

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IT IS well known that in patients with pernicious anemia, adequate therapy with desiccated stomach, whole liver and liver extracts for oral use, or with crude or refined liver extracts given by injection, will arrest the progress of combined system disease and may bring about a variable amount of recovery of nervous function, depending on the duration and severity of the process.[1] Since in many patients the neurologic and hematologic manifestations of pernicious anemia differ strikingly in degree, the possibility exists that these abnormalities are due to deficiency of two different substances, both of which are contained in the therapeutic agents listed above. The frequent development or relapse of neurologic lesions in spite of favorable hematologic response or maintained normal hematologic status in patients with pernicious anemia under treatment with synthetic pteroylglutamic acid,[2] presumably a single pure substance, lends additional support to the possibility that the neurologic and hematologic disorders arise from different deficiencies.

A crystalline substance, vitamin B_{12}, has recently been isolated from liver extracts[3] and found to produce hematologic remissions in pernicious anemia.[4] An unusual opportunity for testing the effectiveness of vitamin B_{12} upon the neurologic disturbance of pernicious anemia presented itself in a patient who had developed acute combined system disease while receiving hemopoietically inadequate doses of synthetic pteroylglutamic acid. The patient also had an acquired allergic sensitivity to injected liver extracts. It was of additional interest, therefore, to determine the relation of vitamin B_{12} to this sensitivity.

TABLE 1. *Results of Vitamin B_{12} Therapy* in a Patient with Combined System Disease and Pernicious Anemia.*

DAY OF THERAPY	PINPRICK SENSATION		VIBRATION PERCEPTION	ATAXIA	ROMBERG'S SIGN
	FINGERS	FEET			
1	Impaired, index and middle fingers	Impaired, distal to ankles	Absent at toes, ankles, tibias, patellas and below 2nd lumbar segment	+++	++
6	Normal	Impaired, distal to ankles	Absent at toes, ankles, tibias, patellas and below 2nd lumbar segment	+++	++
10	Normal	Impaired in toes	Present in right patella	+	+ (after 8 sec.)
13	Normal	Slightly impaired in toes	Present in 3rd lumbar segment, both patellas and right tibia	±	Sway (after 30 sec.)
19	Normal	Impaired in toes	Absent in left patella, both tibias and feet	±	Patient fell after 10 sec.
23	Normal	Slightly impaired in great toes only	Present in both patellas and both tibias	±	Patient fell after 10 sec.
60	Normal	Normal	Present in right internal malleolus	None	Negative

*Therapy consisted of 5 microgm. intramuscularly each day for eight days. Treatment was omitted from the ninth through the fifteenth day and resumed (in doses of 5 microgm. three times a week) from the sixteenth day onward.

CASE REPORT

A 41-year-old mulatto woman entered the hospital on May 26, 1948, because of ataxia. She had been admitted to the hospital because of anemia 6, 4 and 2 years previously. Histamine-fast achlorhydria was demonstrated repeatedly, and at the first two admissions she showed adequate hematologic and clinical response to the injection of purified liver extracts. After she had received injections of liver extracts derived from pork for 9 months without discomfort, she experienced generalized urticaria and itching after each of two such injections. Relief followed a change of therapy to beef-liver extract. After receiving the latter for 10 months the patient began to react to this substance also. Positive skin tests to both pork and beef extracts were demonstrated, nine different commercial liver preparations being used. Consequently, on the third admission in September, 1946, she was treated intramuscularly with synthetic pteroylglutamic acid (folic acid) in doses of 10 mg. daily for 10 days, again with typical hematologic and clinical responses. No neurologic changes were demonstrable at any of the three admissions.

Before discharge from the hospital she received four doses of folic acid, 75 mg. each intramuscularly at intervals of a

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week. After discharge she attended irregularly for injections, and hence received an average of only one each month for the next year. Because of failure to reach normal blood values she was started on 50 mg. of folic acid orally daily on September 9, 1947, and she continued to take this amount until the end of the year. At about Christmas time she developed some numbness and stiffness of the hands, together with difficulty in their use for finer motions. This lasted 4 or 5 weeks and then disappeared completely. From this time she took folic acid irregularly, sometimes averaging one dose of 50 mg. every other day, but at other times omitting therapy for periods up to 1 week when her supply of medicine ran out.

Apart from some throbbing in the upper part of the chest she felt well until 1 week before entering the hospital. At that time, while walking in the street, she suddenly experienced a sensation of pressure about the upper abdomen as if she were wearing an elastic girdle, and at the same time her gait became unsteady. These symptoms persisted with some fluctuation in severity. Her legs felt numb from the knees down, and she had to be helped to the hospital by two friends because of the difficulty in walking.

Physical examination showed a pale, well nourished woman with normal findings except on neurologic examination, which revealed gross ataxia with positive Romberg's sign and defective position sense and pinprick perception in the toes. There was absence of vibratory sensation in the lower extremities. movements of the ankle, the knees and the fingers. Vibration sense, as tested with a heavy tuning fork (128 double vibrations), was slightly diminished in the middle and index fingers of both hands, absent over the sacrum and spinous processes below the second lumbar segment and only faintly perceived with maximum vibration applied to the iliac crests. Maximum vibration was not perceived in the patellas, tibias, ankles or feet.

On the 3rd hospital day, as a test of sensitivity, the patient was given a single intradermal injection of 0.01 cc. (0.15 *U. S. P.* units injectable) of a pork liver extract in one forearm. This led to a severe and massive local reaction involving the entire volar aspect of the forearm and lasting 4 or 5 days. There was also a systemic reaction in the form of wheals on the opposite forearm and a choking sensation, relieved by 0.5 cc. of 1:1000 solution of adrenaline hydrochloride.

On the fifth hospital day treatment was started with injections of vitamin B_{12}* in doses of 5 microgm. daily for a total of eight injections, the first being given intradermally, and the subsequent ones intramuscularly. The intradermal injection was given in 0.2 cc. of physiologic saline solution, producing a wheal that reached a maximum size of 2 cm. in 30 minutes and subsided entirely in a few hours. No systemic symptoms followed the intradermal or the subsequent intramuscular injections of vitamin B_{12}, each of which contained 5 microgm., an amount approximately forty-five times as great as that contained in the 0.01 cc. of liver extract tested.

TABLE 1. (*Continued.*)

Day of Therapy	Position Sense	Plantar Reflexes		Tendon Reflexes	Numbness	
		right	left		hands	feet
1	Absent in toes	Extensor from outer border of foot	Poor flexor (equivocal) from outer border	Greatly increased	Present	Distal to both ankles
6	Absent in toes	Extensor	Flexor	Increased	Absent	Distal to both ankles
10	Absent in toes	Flexor	Flexor	Normal	None	In toes
13	Inaccurate for slight movements of toes only	Flexor	Flexor	Normal	None	In toes
19	Inaccurate for moderate and slight movements of toes	Flexor	Flexor	Increased	None	In toes
23	Inaccurate for very slight movements of toes only	Flexor	Flexor	Normal	None	In great toes only
60	Inaccurate for very slight movements of toes only	Flexor	Flexor	Normal	None	Very slight in right great toe only

The plantar responses were of flexor type. The day after entering the hospital she noticed numbness of the tips of the index and middle fingers, and examination demonstrated hypalgesia at these sites.

Examination of the blood disclosed a red-cell count of 1,920,000, with a hemoglobin of 6.5 gm. per 100 cc. (42 per cent), a mean corpuscular volume of 104 cubic microns, a mean corpuscular hemoglobin concentration of 32 per cent and a mean corpuscular hemoglobin of 33 micromicrogm. The reticulocytes were 0.6 per cent, and the white-cell count was 2200.

The patient was placed on a diet free of meat, fish and eggs. Folic acid was discontinued, and no antianemic therapy was given for the first 4 days. On the 4th hospital day she was grossly ataxic in walking, requiring continued support and assistance. When she stood with the eyes open she swayed, and when the eyes were closed she fell backward within 10 seconds. There was no affection of vision, and the optic disks were normal. The hands were used clumsily, but there was no weakness. The tendon jerks in the upper limbs were all very brisk — the right more than the left. The lower limbs were ataxic in heel-shin tests but were not weak. The knee and ankle jerks were very brisk, and the left ankle jerk was more increased than the right. The right plantar response was extensor from the outer border of the foot, and flexor from the inner. Sensation to pinprick was diminished over the two distal phalanges of the fingers of both hands and distal to both ankles. No loss of sensation to cotton wool could be found in any part. The muscles were not tender. Sensation of position was absent in both great toes, but was present for gross

The reticulocytes began to rise on the 4th day of treatment and reached a peak of 16.0 per cent on the 6th day. By this time the patient felt well and displayed an excellent appetite. After 10 days of vitamin B_{12} therapy the red-cell count and the hemoglobin had risen to 2,840,000 and 9.0 gm. per 100 cc. (58 per cent), respectively.

Remarkable changes in the neurologic disorder were already evident by the 10th day of treatment. The recent numbness of the fingers and clumsiness in using them had vanished by the 4th day. On and after the 6th day of treatment an extensor plantar response was rarely obtained. By the 10th day the patient could walk without support, with only occasional unsteadiness, the tendon reflexes were of normal amplitude, and the plantar responses were both clearly flexor. By the 13th day mild vibration was appreciated in the right patella, and maximum vibration was perceived in the right tibia and left patella.

Beginning on the 9th day after the start of therapy, treatment with vitamin B_{12} was discontinued for 7 days because of delay in obtaining a further supply of the material. After the 13th day there was a slight setback in the neurologic improvement, so that by the 19th day there was a reversion of neurologic signs to their status of the 6th and 10th days. This finding was reported by the neurologist without his knowledge of the lapse in treatment.

Treatment was reinstituted on the 16th day in doses of 5 microgm. of vitamin B_{12} intramuscularly three times a

*Kindly supplied by Dr. Augustus Gibson, of Merck and Company, Rahway, New Jersey.

week. By the 21st day further improvement was already appreciable. Vibration sense had been regained in both tibias, as well as in both patellas, and the tendon reflexes had returned to normal. By this time also hypalgesia had become difficult to demonstrate, position sense was remarkably accurate and the gait showed only a slight falter. From then on progress was slower. Sixty days after the beginning of treatment, the patient's gait was natural and she was able to stand with eyes closed without swaying. There was still slight numbness of the right great toe, but not elsewhere. The plantar responses were both clearly flexor, the tendon jerks were of normal amplitude, and there was doubtful, if any, disorder of sensation to touch or pinprick. Sense of position was acute in all extremities except for appreciation of very small movements in the right great toe and small movements in the left great toe. Vibration was just appreciated over the internal malleolus on the right side and was readily perceived over both tibias and patellas. The neurologic findings are summarized in Table 1.

On the 24th day the red-cell count had reached 3,380,000, and the hemoglobin 10.2 gm. per 100 cc. (65 per cent).

Discussion

In view of the fact that marked anemia was present at the time of the development of the neurologic symptoms, it is difficult to decide whether the neurologic disturbance occurred as a natural event in the history of the disease or whether its development can be attributed to the previous synthetic pteroylglutamic acid therapy. Although the neurologic findings were entirely consistent with the presence of combined system disease, it is possible that the improvement may have been due simply to the cessation of folic acid therapy at the time of entry. Against such an explanation is the progression of the neurologic lesion during the first four days under observation and the rapid and extensive improvement following the initiation of vitamin B_{12} therapy on the fifth hospital day. Especially significant is the slight setback during interruption of vitamin B_{12} therapy with further recovery after its resumption.

These findings indicate that, as with previous stages in the purification of liver extract, the achievement of a crystalline derivative with intense hemopoietic activity has not diminished the ability of the material to arrest and in part to reverse recent neurologic manifestations of pernicious anemia.[1,5] The dramatic changes in this patient strongly suggest that a deficiency of vitamin B_{12} is closely related to the natural origin of both the blood and the nervous changes. They should not be interpreted to mean that vitamin B_{12} was more effective than treatment with liver extract would have been.

It is evident that the neurologic lesion in this patient was in great part reversible, exemplifying the stage of "biochemical lesion" that precedes the structural degeneration of the spinal cord. The experience recorded above emphasizes the well known fact that spinal-cord symptoms of combined system disease constitute a medical emergency. The longer the lesion has existed, the more difficult it is to reverse.

The findings in this case also suggest that allergic sensitivity to liver extract is due not to sensitivity to the active principle itself but to other material in liver extracts, with species specificity, as demonstrated by Bauer and his co-workers.[6]

Summary and Conclusions

In a patient with pernicious anemia in relapse and acute combined system disease that developed during irregular treatment with synthetic pteroylglutamic acid, a hematologic remission and rapid and marked improvement in the neurologic picture followed treatment with crystalline vitamin B_{12}. The patient showed severe local and systemic sensitivity reactions to purified liver extracts derived from both pork and beef, but not to vitamin B_{12}.

The findings in this patient suggest that vitamin B_{12}, like the presently available injectable liver extracts, should prove effective against the neurologic as well as the hematologic manifestations of pernicious anemia. They also suggest that vitamin B_{12} is not responsible for sensitivity reactions to liver extracts.

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CONDITIONED-REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Results Obtained in 2323 Net Cases from 3125 Admissions Over a Period of Ten and a Half Years

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THE conditioned-reflex treatment of chronic alcoholism, as employed at the Shadel Sanitarium, consists of establishing an aversion to the sight, taste, smell and thought of all types of alcoholic beverages. This is accomplished by repeated conditioning seances, which may number four to eight before the desired aversion is established.

An individual seance consists of the administration of a nauseant drug, emetine, which, acting as the unconditioned stimulus, elicits an unconditioned reflex. Immediately before the onset of nausea a patient is given various types of alcoholic beverages (the conditioned stimulus). After the repetition of several such seances a conditioned-reflex aversion against all types of alcoholic beverages is developed, and the patient has a deep and lasting aversion to the sight, taste and smell of each. Details of technic have been published elsewhere.[1–4]

From the middle of 1935 to the end of 1945 there were 3125 admissions for the treatment of chronic alcoholism. These were unselected cases. No patient was refused treatment except for physical incapacity, psychotic tendencies or obvious insincerity. Patients treated subsequent to 1940 were offered a year's reinforcement program[5] — that is, the initial conditioned reflex was reinforced by periodic single conditioning seances for a year after treatment.

These 3125 cases represented people from all walks of life. Social status ranged from the very rich to the very poor — from the highly trained professional man to the former inmates of state institutions. Practically every type of labor, trade and profession was represented, indicating that alcoholism is no respecter of person, class or intelligence. The ages ranged from twenty to seventy-eight years. The vast majority of the patients, however, fell into the age group from thirty-five to fifty-five. Ninety-three per cent of the patients were men. Indications are, however, that the percentage of women will be higher in the future series. Types of personalities varied from the well adjusted business or professional man to the more severe type of psychoneurotic.

The treatment is a safe procedure if administered by properly trained personnel. There were only 3 deaths that might be associated with the treatment. Of these, one resulted from congestive heart failure, and 2 from coronary occlusion. Its wide applicability is seen in the fact that only 32 patients, or approximately 1:100, were believed unfit physically to take the treatment. The only intellectual requirement was that the patient not be psychotic and that he be sincere in wanting to overcome his problem.

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ESTABLISHMENT OF NET CASES

Of the 3125 patients admitted during this period, 304 did not complete treatment. Of these 135 refused to accept treatment after sobriety was established, 32 were refused treatment because of physical disabilities such as severe heart disease, advanced arteriosclerosis and perforating ulcer, 31 refused to complete treatment after it was begun, and 13 were refused treatment because of psychotic symptoms or obvious insincerity. The reason for not giving treatment to 86 patients was not shown on the hospital records. There were 7 deaths in this group; 4 were secondary to delirium tremens, and 3 were considered secondary to the treatment. Patients who could not be traced numbered 448. In 50 patients who died before the closing of this survey the cause of death was also classified as "unknown" even though they were sober at the time of death. This was necessary for statistical purposes because it could not be said that they would have remained sober until the close of the survey. There were, therefore, 2323 patients who were treated and whose status was definitely known at the closing date of the survey.

RESULTS

The tabulated data showing the percentage of abstinence among the net cases are presented in Figure 1. Continuous and complete abstinence from alcohol in any form, from the time of treatment until the closing date of the survey, was necessary for the patient to be classified as abstinent. Of the 2323 patients treated over the previous ten and a half years 1042, or 44.8 per cent, were found to be abstinent at the close of the survey in 1945. An additional 92 patients were retreated a short time after relapse and remained abstinent, giving an over-all figure of 48.8 per cent for the entire series.

A better understanding of the effects of time on the abstinence ratio can be had if the ten and a half years are divided into twenty-one periods of six months each as shown in Figure 1. From this it can be seen that about 85 per cent will remain abstinent for six months, about 70 per cent will remain abstinent for a year, 60 per cent will remain abstinent for

two years, about 55 per cent will remain abstinent for three years, about 40 per cent will remain abstinent for four years, over 30 per cent will remain abstinent up to seven years, and about 25 per cent will remain abstinent up to ten and a half years or longer.

While the data pertaining to the results obtained were being compiled a more comprehensive analysis

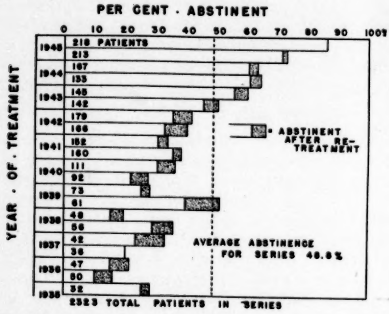

FIGURE 1. *Abstinence (Percentage) for Each Six-Month Period from the Middle of 1935 to the End of 1945.*

The number of patients in each group is also shown. The stippled area represents an additional percentage obtained from 92 patients who remained abstinent as a result of retreatment shortly after relapse.

of the patients in this series was carried out. A full analysis of these findings will be reported elsewhere.[6] Many salient factors influencing prognosis in the alcoholic patient were brought out by this analysis.

Such factors as marital happiness, occupational success, intelligence, financial security, interest in sobriety clubs, good co-operation and emotional stability were indicative of good prognosis, whereas marked nervousness, even when the patient was sober, a history of recurrent delirium tremens, instability about occupation, financial indolence and alcoholism under thirty years of age indicated a poorer although not a hopeless prognosis.

This group of patients is believed to be one of the largest reported from a single source in the United States. Except for varying amounts of field rehabilitation, conditioned-reflex therapy was the only treatment that these patients received for their alcoholism. In our opinion the gratifying results obtained definitely prove the inherent value of conditioned-reflex therapy in the treatment of this disease. Even in patients who relapsed it was definitely worth while from both an economic and a social standpoint. This is better demonstrated in Table 1.

For example, 94 patients remained totally abstinent for more than 30 months before they relapsed. Three hundred and twenty-one remained totally abstinent from 6 to 30 months. An average period of 11.2 months of abstinence was obtained in this group of relapsed patients. A total of 9715 man months, or 809 man years, of total abstinence was accomplished among the relapsed patients. Many have since been retreated and are sober but are not included as successful cases.

Another advantage of the conditioned-reflex treatment is the easy manner in which it blends with adjuvant therapies. This is particularly true of psychotherapeutic approaches, such as an interview under pentothal narcosis.[7] In assisting the patient to remain abstinent while a program of environmental and personality adjustment is carried out, conditioning therapy renders a valuable assistance to the psychotherapist. Of significance in the analysis of the relapsed patients is the fact that 30 per cent of the patients admitted had apparently been in need of psychotherapy. This was determined in a study of the "reasons" for relapse among these cases.

Since the close of this survey approximately 2000 additional cases have been treated. Many of these patients have been and are being given adjuvant forms of therapy in addition to the conditioned reflex. This includes pentothal narcoanalysis and psychotherapy, intensive physical and social rehabilitation and, in a very few selected depressed cases, shock therapy. It is hoped that this additional therapy and evaluation will improve the prognosis in the alcoholic patients as well as encourage the use of a more comprehensive therapeutic program elsewhere.

TABLE 1. *Period of Abstinence in Patients Who Again Began to Drink after Treatment.*

PERIOD OF ABSTINENCE AFTER TREATMENT	NO. OF PATIENTS	PATIENT MONTHS*
mo.		
Less than 1	97	0
1	54	54
2	74	148
3 to 6	228	1140
7 to 12	139	1350
13 to 18	84	1344
19 to 24	72	1584
25 to 30	26	728
31 to 36	19	627
36 and over	75	>2700
Totals	868	9715†

*Number of patients multiplied by months of abstinence.
†Or 809 man years.

SUMMARY AND CONCLUSIONS

Statistical evaluation of 2323 net cases treated by conditioned-reflex methods over a period of ten and a half years and data concerning 3125 admissions are presented.

Eighty-five per cent of patients treated by this method will remain abstinent for six months or longer; 70 per cent will remain abstinent for a year; 60 per cent will remain abstinent for two years;

about 55 per cent will remain abstinent for three years; 40 per cent will remain abstinent for four years; 30 per cent will remain abstinent for seven years; and 25 per cent will remain abstinent up to ten and a half years or longer.

The treatment is of definite benefit both economically and from a social standpoint, even for patients who have relapsed. The relapsed patients remained abstinent for an average of slightly more than eleven months before resuming drinking.

The results obtained prove, beyond all reasonable doubt, the inherent value of this treatment. Adjuvant forms of therapy have been used more extensively since this survey has ended. Their ultimate value, however, has as yet not been fully determined.

Factors such as age, occupational stability, marital unhappiness, nervousness, history of recurrent delirium tremens and financial indolence have a definite effect upon the prognosis, either favorable or unfavorable. Further studies of these influences may prove of value in determining the type and extent of treatment necessary in the individual case.

These patients closely represented a cross section of humanity from an occupational and social standard as well as personality types. The wealthy, the middle class, the poor and the gamut of all classifications of character types were amply represented.

It is hoped that the conditioned-reflex will be utilized more widely and combined with other forms of therapy in selected cases since it assists therapists by helping the patient remain abstinent while a program of personality and environmental adjustment is carried out.

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MEDICAL PROGRESS

PREGNANCY TESTS*

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IT IS remarkable that a condition so essentially benign and self-limited as pregnancy, which must inevitably become obvious in the due course of time, has evoked so much interest in its early diagnosis. Despite the fact that in all but possible ectopic pregnancies no great need for speed in diagnosis truly exists, constant emphasis has been attached to the time required for the performance of a pregnancy test. As a result, although the first modern pregnancy test, the Aschheim–Zondek, which was described approximately twenty years ago, has never been surpassed for accuracy, new procedures have appeared each year, designed essentially to cut down the time required for a diagnosis. In addition, the practice of attaching the name of the investigator to each modification of an established test has created so many new tests that intimate knowledge of each is now virtually impossible for any one person. In general, however, the great variety of procedures fall either into one of several well defined categories, such as biologic assays, chemical assays and skin tests, or into a heterogeneous group, which is composed of such procedures as white-cell counts, biopsy technics and others.

It is the purpose of this paper to review critically the historical development of present-day pregnancy tests and to discuss briefly tests that have gained acceptance by clinical trial as well as those that bear promise for the future. Accepted or new technics now in current use are discussed individually, their modus operandi being emphasized. It is perhaps well to state at the outset that no perfect pregnancy test exists and that it is certainly impossible to select any one of the existent procedures described below as best. However, in considering the advantages and disadvantages of each, it is hoped that the specific value of each technic will be better appreciated and its place in pregnancy diagnosis more clearly defined.

Historical Review

From existing translations of Egyptian papyri it is evident that tests for pregnancy were per-

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formed as long as four thousand years ago.[1] Although many of the procedures advocated were mystical and apparently bizarre, one basic concept, intelligible from modern standards, arose in these early times and persisted to the sixteenth century — namely, the idea that urine from pregnant women stimulated plant growth. These pregnancy tests based on the stimulation of plant growth and germination of seeds are still occasionally referred to in the relatively recent literature and have therefore been used for several thousands of years.

Although the search for improved methods was constant, it was only in the early twentieth century that the pioneer work of Evans and his associates,[2] Smith and Engle[3] and Zondek and Aschheim[4–6] made possible the present era of accurate pregnancy diagnosis. The demonstration by these authors of the complex inter-relation between the ovary and the pituitary body and the urinary reaction of these hormones produced for the first time the tools necessary for basing pregnancy diagnosis on sound scientific grounds. In 1928 the epochal description of the Aschheim–Zondek[6] test appeared, reactivating interest in rapid, accurate diagnostic tests of pregnancy.

Diagnostic laboratory procedures suggested by Abderhalden,[7] Kamnitzer[8] and Roubitschek[9] antedated somewhat the Aschheim–Zondek test. However, by present standards, these tests were grossly inadequate and have long since been mostly forgotten.

The Aschheim–Zondek test provided, for the first time, a means of diagnosing early pregnancy that was almost 100 per cent accurate. Its accuracy remains unsurpassed to this day. Since the description of this pioneer test, many variants have been proposed, all designed to cut down the time required for the performance of the test. The Friedman test,[10] originating two years after the Aschheim–Zondek test, represents a simple modification employing isolated female rabbits. With the use of this animal the time required for obtaining a diagnosis was cut from five to two days.

Despite the widespread adoption of the Friedman test and its high degree of accuracy, the time element that it required remained a compelling force for further improvement. In 1933 Shapiro and Zwarenstein[11] presented before the Royal Society of South Africa a new test for pregnancy, utilizing for the first time an amphibian, the female South African clawed frog (*Xenopus laevis*). The time for a reaction was reduced to within twenty-four hours, but the unavailability of the frog unquestionably blocked, to some extent, the widespread adoption of this technic. However, this very valuable observation — namely, that amphibia would react to mammalian hormones — served as the forerunner of other frog tests, described below.

With the knowledge that hyperemia is one of the first detectable changes produced in the ovary of infantile rats by gonadotropins, numerous investigators have adopted this tissue change as a criterion for a positive pregnancy reaction.[12–21] Starting with procedures advocated by Eberson and Silverberg[12] and Reiprich,[13] in which the hyperemic change was read at an approximate twenty-four-hour interval, use as an endpoint earlier and more subtle color differences, the time has been reduced to two hours, in the form of the Kupperman–Greenblatt[21] test. As might be anticipated, however, as the time for reading the reaction has been shortened, the color changes have become more and more slight. This difficulty in reading the endpoint constitutes a serious block to the widespread acceptance of this technic.

Within the past two or three years a totally new method of pregnancy diagnosis has developed, utilizing male frogs. It was shown by Robbins and Parker[22] that the reaction of the male frog to gonadotropic hormone could be easily demonstrated by microscopical examination of cloacal fluid. The appearance of sperm indicated a positive reaction. Perhaps even more significant, however, was the fact that this reaction occurred quickly, usually within the four-hour period following the administration of the hormone. The use of this reaction for a diagnostic test for pregnancy was obvious, and within the past year Mainini[23] has suggested a technic using a South American species of toad (*Bufo arenarum hensel*), and soon thereafter Wiltberger and Miller[24] and Robbins and Parker[25] demonstrated that the common North American frog (*Rana pipiens*) was equally suitable.

By the use of the *Rana pipiens*, laboratory diagnosis of pregnancy could be carried out within two hours, frequently sooner, and the endpoint was absolutely clear cut, sperm being either present or absent. From these early experimental reports, it appears that the procedures have great promise, offering economy and speed as well as accuracy. How well they will stand up under widespread clinical trial remains to be seen.

Chemical procedures capable of performance in a test tube and obviating the inconveniences of animal tests have long been sought. The urinary histidine test, reported by Voge[26] soon after the original description by Aschheim–Zondek, more recently studied in great detail by Kapeller–Adler and Haas,[27–29] has not achieved wide acceptance. Young,[30] Seidman[31] and Krieger,[32] among others, doubted its value since it fell far short of the accuracy of the Aschheim–Zondek test and, moreover, had little value for the diagnosis of early pregnancy, being of chief value in the later stages of pregnancy. The Visscher–Bowman[33] test, a color reaction that was first described in 1934, appears, in the light of clinical trial, to have little usefulness.

Frech,[34] Sheehan[35] and Hadley[36] have reported that the difficulty in reading the endpoint was considerable and, moreover, that the specificity of the reaction was open to grave doubt, positive reactions having been obtained by the simple addition of sugar to the urine.

The colorimetric test of Schmulovitz and Wylie,[37] based on the detection of estrin in the urine, appears also to be of limited value, since according to Pincus[38] it is not reliable in early pregnancy when estrin titers are frequently low.

Fairly recently a colorimetric test has been described by Guterman.[39] It is based on the observation by Venning and Browne[40] that pregnanediol (an excretion product of the corpus luteum hormone) is excreted in the urine of pregnancy in increasing amounts throughout gestation. Too little time has elapsed since the advent of this technic to permit adequate evaluation; however, several reports have appeared suggesting that its accuracy is below that of the Aschheim–Zondek test or its Friedman modification, and, moreover, false-positive tests may occur under conditions of delayed menstrual periods.[41, 42] Notwithstanding these reports, this chemical test for pregnancy, free of the encumbrances of the use of animals and based on sound endocrinologic principles, merits careful evaluation.

Other technics too numerous to mention have been devised for the laboratory diagnosis of pregnancy. None of them have successfully stood the rigid test of clinical trial, and they have therefore never gained any universal acceptance. For the sake of completeness alone, perhaps the following few merit mention. Prostigmin has been administered in problems of delayed menstruation on the hypothesis that prostigmin "will induce menstruation in a nonpregnant woman and should no menstruation occur, the woman is invariably pregnant."[43] Several skin tests have been advocated, on the assumption that the reactions that develop will serve to differentiate pregnant women from nonpregnant women. Placental extract,[44] colostrum[45] and antuitrin-S[46] are some of the most commonly used agents. In the placental test the pregnant woman reacts more strongly to the antigen, and in the antuitrin-S and colostrum tests the reverse is true. Although these last few tests receive sporadic attention in the literature, it is fairly well agreed that to date they are not totally reliable.

From this historical review it is evident that great strides in the diagnosis of pregnancy have been made; however, a test for pregnancy that is 100 per cent accurate and capable of being performed in a test tube within a few minutes has yet to be found.

Fundamental Physiology

Basically all the common pregnancy tests, such as the Aschheim–Zondek, Friedman, rat hyperemia and frog tests, consist of animal assay methods of detecting the high levels of hormone produced during pregnancy. Hence, they rest upon two fundamental facts: that during pregnancy there is an increase in either the production or the excretion of these hormones, and that these hormones produced by the human female will effect demonstrable changes in lower animals.

Present knowledge of the endocrinology of pregnancy has undergone many changes and much

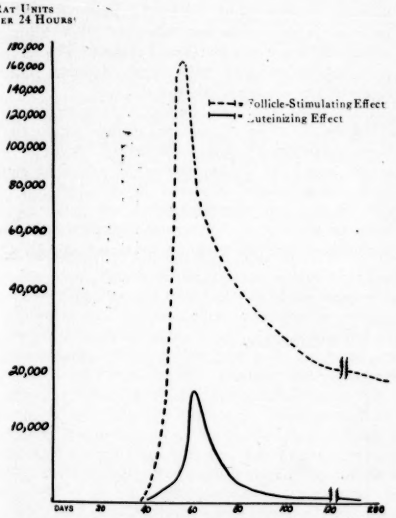

Figure 1. *Urinary Excretion of Chorionic Gonadotropin during Pregnancy (Assayed on Rats).*

development, but at present it is clear that the gonad-stimulating substances demonstrated in the urine of pregnant women by the Aschheim–Zondek test are at least largely of placental origin.[47–49] Direct evidence of the formation of gonadotropin by placental cells was obtained by Jones, Gey and Gey,[50] who assayed this hormone from serially transplanted tissue cultures of these cells, in which the final explants were composed entirely of cells grown in vitro. Although differences exist, this gonadotropin of placental origin is virtually identical with that of pituitary origin — hence the old designation anterior-pituitary-like (APL).[48]

The problem of whether this placental secretion is composed of one or two hormones similar to the pituitary follicle-stimulating hormone and luteinizing hormone is beyond the scope of the present paper. Aschheim and Zondek demonstrated clearly

that two distinct changes occurred in the ovaries of the rat after the administration of urine from a pregnant woman. These organs responded either to two different hormones or to one hormone in two different ways, first by follicle formation and secondly by luteinization and the development of corpora lutea. As a result, when the rat is used for the determination of the titer of placental hormone during pregnancy two distinct endpoints must be followed, producing as it were two separate curves for gonadotropin production during pregnancy. The first endpoint is reached at the highest dilution of the urine that will produce definite corpora lutea formation. Beyond this dilution definite follicle formation is still present. The second endpoint is reached only when definite follicle formation is extinguished (Fig. 1).

From this graph it can be seen that there is a considerable lag after conception, during which little hormone production can be detected. A rapid rise ensues, to a peak at approximately seven or eight weeks of gestation, followed by a rapid fall, so that in the last trimester levels of gonadotropic hormone are low. It is, therefore, perfectly possible to obtain a negative pregnancy reaction during the

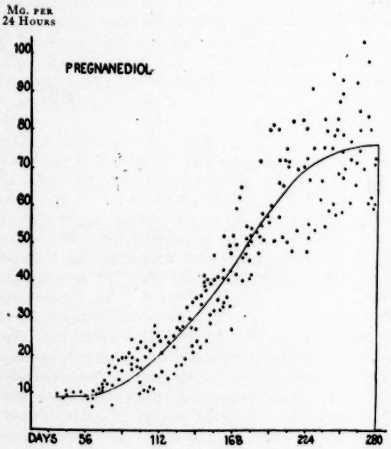

FIGURE 2. *Urinary Excretion of Pregnanediol in 8 Cases of Normal Pregnancy (Reproduced from Fenning[83] by Permission of the Publishers).*

last trimester in the obvious presence of a living fetus. It is, moreover, very important to note that the follicle-stimulating effect begins first and is well marked at a time when virtually no luteinizing effect is present, and that it remains at a much higher titer throughout pregnancy. The importance of these facts is brought out below in a consideration of the so-called weakly positive test.

Other hormones produced in increased amounts during pregnancy are estrogen and progesterone, the latter forming the basis of an important chemical pregnancy test, the Guterman test for pregnanediol. Ample evidence exists to establish the fact that the placenta, in both man and animals, as well as the ovaries, forms these substances.[51,52] In fact, in the last months of the gestation, after the corpus luteum of the ovary degenerates, the placenta is the chief source of progesterone. Unlike the gonadotropins, these substances show progressively rising titers throughout the period of gestation and pass through no peak, abruptly falling either shortly before or at the time of delivery. Since the progesterone elimination almost exactly parallels the estrogen excretion, a curve of the latter substance will suffice to show the distribution of both hormones during pregnancy (Fig. 2). It is therefore apparent that excretion of progesterone — that is, pregnanediol — will be least in the early stages of pregnancy and progressively more well marked in the later stages.

That pregnancy hormones will produce changes in lower animals is now well known.[54,55] Zondek and Aschheim[54,55] have classified the ovarian changes produced by gonadotropins as follows:

APR I — follicle ripening and induction of vaginal estrus.
APR II — hyperemization of ovary and follicle hemorrhage.
APR III — formation of corpora lutea.
(APR = anterior pituitary reaction.)

These gonadotropic reactions occur in a fixed sequence, with relatively fixed time relations, dependent only on the species of animal used, the type of hormone and the route of administration of the hormone. That is to say, the size of the dose and conditions of maintaining the animal have relatively no effect on the speed of the reaction. The first gross effect is hyperemization of the ovary; shortly therafter, swelling, followed by ovulation, occurs, in turn followed by lutea formation. Up to recent date, the three animals most widely used for laboratory diagnosis of pregnancy have been the mouse, rat and rabbit. Each of these animals reacts in its own more or less charactistic fashion to the administration of gonadotropic hormone — the mouse and rabbit by the formation of corpora hemorrhagica, and the rat by the formation of cystic follicles that later become luteinized. Follicle hemorrhage or corpora hemorrhagica are rarely seen in the rat. Moreover, it is also known that the congestion and reddening of the ovaries (APR II) is most readily seen in the rat, the only animal in which the ovaries, at rest, are quite anemic. Species differences in sensitivity to chorionic hormone also occur thus; for a given weight, immature rats are twenty-five times more sensitive to chorionic gonadotropin than mice. The rabbit in turn is more sen-

sitive than the rat or mouse, on a gram for gram basis; however, its large bulk necessitates such large dosage of hormone that its relative sensitivity is of little practical advantage.

As for the frog, work is still in the developmental stage. However, it appears that the female *Xenopus laevis* as well as the male *Bufo arenarum* and *Xenopus laevis* respond to the luteinizing hormone of the chorionic gonadotropin, the first by the extrusion of the ova, and the last two by the emission of spermatozoa. Although there are other substances to which the frogs will react, they do not interfere with the use of these animals for pregnancy diagnosis, since they are never encountered in the course of pregnancy.

Mainini[23] states that the *Bufo arenarum hensel*, the South American toad advocated by him for pregnancy diagnosis, will react to 40 international units of gonadotropin. From work performed in this laboratory[56] it appears that the average male *Rana pipiens* will react to the same dose of chorionic gonadotropin as the average immature rat; this apparent equal sensitivity, it should be noted, is not based on weight equality. However, it is of practical significance since it makes the individual *Rana pipiens* able to detect levels of hormone that up to now could only be detected by rats.

From the preceding brief summary it can be seen that the choice, performance and evaluation of a pregnancy test is not a simple matter. The choice of animal, in relation to the specific hormone to be assayed, is of great importance. The speed with which the target organ can react is constant and therefore predetermines the speed of the test, a factor of great importance in problems of therapy. The species sensitivity is of obvious significance, especially when one is dealing with hormone titers away from the peak period of elimination of hormone. Thus the immature rat becomes the animal of choice in urines or serums of probable low hormonal titer, especially when the titer of the pregnant urine is so low as to produce only follicle stimulation without the production of true corpora lutea.

Common Tests

A list of pregnancy tests in use or developed during the past ten years is as follows:

Bio-assay technics:
- Rodents:
  - Aschheim–Zondek technic.[6, 51, 57–59]
  - Ovarian hyperemic test.[12–21]
  - Ovulatory test.[60]
- Rabbits:
  - Friedman test.[10, 61–64]
- Amphibia:
  - Female *Xenopus laevis*.[11, 65–69]
  - *Bufo arenarum hensel*.[23]
  - *Rana pipiens*.[24, 25]
- Fish tests.[70]

Chemical tests:
- Histidine tests — Kapeller-Adler.[27–29, 71, 72]
- Visscher–Bowman test.[33, 73, 74]
- Colorimetric test — Schmulovitz–Wylie.[37]
- Pregnanediol test — Guterman.[39, 75–77]

Skin tests:
- Colostrum.[48, 78, 79]
- Placental extract (Gruskin).[44, 80]
- Chorionic antuitrin-S test (Gillfillen–Gregg).[46, 80–82]
- Estrogen.[83]

Miscellaneous technics:
- Pupillary test (Bercovitz).[84]
- Prostigmine.[43, 85]

This list by no means includes all the technics developed since the advent of the Aschheim-Zondek test. Rather, it is intended to include either tests in current use, as indicated by the recent literature of the past ten years, or procedures that have appeared in the past ten years and have yet to be evaluated.

Aschheim–Zondek Test[6]

The oldest of all the so-called "modern" pregnancy tests, this remains to date one of the most widely employed and certainly one of the most accurate technics. As originally described it employs immature mice weighing 8 gm. and approximately three weeks of age. Filtered morning urine, in amounts of 1.8 to 2.4 cc., is administered to each mouse in individual doses varying from 0.3 to 0.5 cc. three times daily for two days. Ninety-six hours after the first injection the animals are sacrificed, and the ovaries examined for "blutpunke," or corpora hemorrhagica, a change produced by the presence of chorionic gonadotropin in the urine. In some laboratories the immature rat has been substituted for the mouse because of its greater sensitivity to the hormone and resistance to toxic factors in the urine. Rats twenty-one to twenty-three days old are injected with 6 cc. of urine given in 1-cc. doses twice daily for three days. The animal is sacrificed on the fifth day, and the ovaries examined for follicle formation and corpus luteum formation. Corpora hemorrhagica are rarely found in the rat. In this laboratory, the presence of corpora lutea, indicating the presence of luteinizing hormone, is required as the minimum evidence of a pregnancy reaction. However, as has been described very early in pregnancy, follicle formation may occur alone in the rats' ovaries because the development of a follicle-stimulating effect antedates the appearance of the luteinizing effect in the first few weeks of pregnancy. Hence, in problems of the diagnosis of very early gestation, the follicle reaction, although not definitive, may well be the harbinger of a developing luteal reaction. The same cycle is followed in reverse at the time of delivery or of fetal

death. Hence, the luteinizing effect disappears before all follicle formation is lost. The value of the follicle-stimulating reaction is therefore quite obvious in questions of intrauterine fetal death and missed abortion. It is of importance to remember that elevations of pituitary follicle-stimulating hormones accompany the menopause; hence, any interpretation of these follicle changes in the rat ovaries can only be made against the background of a proper clinical history. By the use of either the immature mouse or rat, the results obtained with the Aschheim-Zondek test are universally reported as excellent. Aschheim,[57] in 1935, cited his accuracy as 98 per cent in positive reactions and 99.5 per cent in negative tests.

Mazer and Goldstein[51] reported on the results of 11 independent groups with correct positive reactions in 94 per cent and correct negative reactions in 97 per cent of the cases. Mack and Agnew[58] likewise compiled a series of 8685 cases tested by the Aschheim-Zondek technic with an accuracy of 96.6 per cent. In this laboratory, where equivocal ovarian changes in the rat are controlled by microscopical section and examination, the accuracy has closely approximated 100 per cent, only one false report having occurred in the past many years.

It is, therefore, not without reason that the Aschheim-Zondek test has remained a constant favorite. Its accuracy, reliability and sensitivity in well trained hands are goals for other procedures to attain. The one drawback to this procedure, aside from the necessity of maintaining rodents of proper size and age, has been the time required for the performance of the test — four or five days. As stated above, this time interval is fixed by the fact that it requires ninety-six hours for the ovaries of mice to form corpora hemorrhagica and one hundred and twenty hours for the rat ovaries to form corpora lutea.[54, 55]

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34351

PRESENTATION OF CASE

A two-and-a-half-year-old girl was apparently well until six days before admission to the hospital when her parents noted that she walked about bent over as if in discomfort and tended to draw the right leg upward. Except for some decrease in appetite and easy fatigability for several weeks she had no symptoms. Her birth and development were uneventful, and she had had none of the usual childhood diseases.

Physical examination revealed a well developed and well nourished child. The heart and lungs were normal. There was no peripheral lymphadenopathy. Largely filling the right abdomen and extending from costal border to below the iliac crest and across the midline at the level of the umbilicus was a firm, smooth, fixed, nontender mass, which was not lobulated.

The temperature was 99.8°F. The blood pressure was 110 systolic, 80 diastolic.

The urine specimen concentrated to 1.014, and there was no albumin or sugar. One white cell per high-power field was seen. The white-cell count was 9800. The serum protein was 7.2 gm., and the nonprotein nitrogen 31 mg. per 100 cc. X-ray studies of the chest, skull and femurs were negative except for some elevation of both sides of the diaphragm. An intravenous pyelogram showed a huge ovoid mass in the right abdomen. This extended well to the left of the spine, and the tip was over the iliac crest. The mass was somewhat lobulated, and there was a suggestion of minute calcium specks at its lower pole. The liver was thought to be displaced upward. Both kidneys were promptly visualized, and the left appeared normal. The right renal calyxes were displaced upward, and the ureter was displaced toward the midline and somewhat posteriorly. The renal drainage was normal.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Gertrud C. Reyersbach: This child obviously had a large right-sided abdominal tumor. We are asked to determine the type. I think it is possible to exclude certain conditions, such as duplication of the bowel, tumor of the pancreas, hydronephrosis, polycystic kidney and tuberculous lymphadenitis, without further discussion. There are no data to indicate that this child had an ovarian tumor. In lymphosarcoma one would expect a somewhat different clinical picture. In the absence of disturbances of the endocrine system we may exclude a suprarenal cortical tumor. Could this mass have been a Riedel's lobe of the liver? There are several reasons not to think so: the mass described was too large, there were signs of general involvement, and an operation was performed.

The history in this case is compatible with several conditions: neuroblastoma, which arises from cells of the sympathetic nervous system and is the most common neoplasm of the abdominal cavity in early childhood; Wilms's tumor, which is a congenital embryonal mixed tumor arising from the kidney anlage; and unattached retroperitoneal embryoma.

All these conditions are malignant and most frequently make their appearance during the first years of life with a peak between the second and third years. Actually this does not quite hold for the unattached retroperitoneal embryoma, which may be discovered later. In neuroblastoma and Wilms's tumor the first thing usually discovered is the abdominal mass, as in this child. The mild constitutional symptoms — namely, anorexia, fatigability, and the lack of cachexia — are typical of all conditions. Likewise, the sudden discovery of a large mass is typical of these conditions. It is due either to the fact that the mass was overlooked previously or that it had grown rapidly in a short while; such rapid growth is sometimes due to bleeding into a Wilms's tumor. The absence of urinary findings and the distortion of the renal pelvis on x-ray study are frequently seen in all three lesions. The unattached retroperitoneal embryoma usually grows on either side of the vertebral column from as high as the fourth cervical segment down to the internal genitalia. Its location is different from the one described here, and it is extremely rare. I am going to exclude it.

In favor of neuroblastoma are the symptoms of anorexia and fatigability, the presence of the mass on the right side, calcification in the tumor as seen on x-ray examination and displacement of the renal pelvis. Against it is the fact that the mass was described as oval and smooth; most neuroblastomas are described as nodular — certainly those that I have seen have been nodular. Also, the patients that I have observed showed anemia and fever at the time the tumor was discovered. This child's temperature was only 99.8°F.

What is in favor of Wilms's tumor? The symptoms of anorexia, fatigability and displacement of the renal pelvis hold for this tumor also, and x-ray evidence of calcification is also described in Wilms's tumor. The mass is smooth and the border well delineated. Against it is the extension beyond the vertebral column.

I think that the child might have either of these two tumors. Both start retroperitoneally, and in this abstract there is a note saying that the mass arose from the costal margin. That puzzles me. I do not know how to interpret it. I do not know whether the neuroblastoma had metastasized to the liver, but I hope that the x-ray films will give some help.

Dr. Stanley M. Wyman: The mass is fairly well outlined, somewhat smooth and slightly lobulated. It extends past the midline to the left, down to the brim of the pelvis as well as upward to the costal margin, approximately filling the entire right midabdomen. The areas of calcification are fairly well seen, particularly in the lower pole of the mass. The film taken after the injection of dye shows good outlining of the right calyceal pattern. An interesting finding is that the calyxes are displaced upward, but show no significant distortion or apparent invasion. The pelvis and ureter follow a relatively normal course. This film is an oblique view showing the mass lying somewhat anteriorly. The left margin can be well outlined, and the mass appears more anterior than posterior. In no film can one outline the lower margin of the right kidney. This mass cannot be differentiated from the kidney shadow, with which it appears continuous. The lateral view adds no appreciable information. The lungs appear clear. The bones as visualized show no evidence of destruction.

Dr. Reyersbach: Do you think that the mass is attached to the liver?

Dr. Wyman: I cannot say. I cannot identify the liver accurately per se. The lower border fades into this mass, and I cannot say whether it is a part of the mass or is overlying it. I cannot differentiate the liver from the mass any more than I can the kidney from the mass.

Dr. Reyersbach: Your statement that the mass appears to lie anteriorly makes me more discouraged. Both Wilms's tumor and neuroblastoma arise from the retroperitoneal space and are posterior. When I read over the abstract I looked up other tumors that would be more anterior, and they are extraordinarily rare. A tumor of a rib would not behave in that way. Any tumor of the liver in childhood is very rare. There is no indication that the child had an echinococcus cyst. Hemangiomas are usually small and probably would be discovered accidentally.

So my diagnosis has to be a malignant tumor arising from the retroperitoneal space and invading the liver.

Clinical Diagnosis

Neuroblastoma.

Dr. Reyersbach's Diagnosis

Malignant tumor arising from retroperitoneal space and invading the liver.

Anatomical Diagnosis

Hepatoma of liver.

Pathological Discussion

Dr. Oliver Cope: The X-ray Department actually favored a diagnosis of Wilms's tumor. The Surgical Service diagnosed it as neuroblastoma. However, we both agreed that it was retroperitoneal. In operating I thought it wise to approach it transperitoneally through the flank. It was not a neuroblastoma and had nothing to do with the kidney. So far as we could determine at operation it was a primary tumor of the liver and it was so large that it gave the impression of a retroperitoneal tumor. It arose in the right lobe of the liver and had grown upward and backward and appeared on the dome of the liver, with normal liver in front. The tumor invaded the left lobe to such an extent that it would be impossible to excise it without also excising the portal vein. Therefore excision seemed impossible in spite of the fact that we could have saved the left hepatic artery. There was no evidence of metastases or of a primary tumor elsewhere. It was such an unusual situation that we asked Dr. Castleman to come to the operation and view it in its entirety. I presented him with a specimen, and that in itself was a major procedure because this was a very vascular tumor and it was difficult to control the hemorrhage.

Dr. Benjamin Castleman: The piece that Dr. Cope gave me was 1.5 cm. in diameter, which was fairly large considering how friable the tumor was. I did a frozen section and thought that the best diagnosis was a primary liver-cell carcinoma, or a hepatoma, rather than a metastasis from a neuroblastoma. Neuroblastoma may metastasize to the liver and produce a large mass. Usually there is more than one tumor nodule. Here the mass seemed to be continuous from right to left. There was no surrounding cirrhosis, which one usually sees with hepatoma in adults, the cirrhosis being the predisposing cause of the hepatoma. That apparently is not true in hepatomas arising in children. I had never seen one in a child but Steiner,[1] who reviewed all the cases up to 1938, was able to collect over 70 cases of primary liver-cell carcinoma in children under sixteen years of age. It is interesting that over half these were in children under two years of age. He reported that there was no cirrhosis associated with these cases, so that the etiology is probably congenital. He described a case in which the hepatoma was present at birth. The hepatomas in children are usually very malignant, and according to Steiner the average duration of life is four months after the tumor is discovered. The resections that had been done in those cases were unsuccessful, although there have been some cases of hepatoma successfully removed both in adults and children. I can recall one that Dr. Sweet[2] removed from a seventy-five-year-old physician. He was seen by Dr. Sweet three years later and found to have nodules in the right upper abdomen, which were probably recurrences or metastases. However, he continued to practice during this three-year period.

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CASE 34352

Presentation of Case

A thirty-six-year-old housewife entered the hospital with the chief complaint of difficulty in breathing.

For sixteen years prior to admission the patient thought she had had slight difficulty in swallowing food. Three years before entry a physician gave her belladonna because of a sensation of "food sticking in the throat." At this same time she began to have right-upper-quadrant postprandial distress, which disappeared when she was placed on a low-fat diet. About three years before entry she first became aware of dyspnea with the exertion of prolonged talking. She disregarded this, however, until eight months before admission, when she had a sudden increase in dyspnea, with loss of the voice. She believed that these difficulties came from the trachea just below the larynx, and found that she was partially relieved if she pulled the skin of the neck forward. The severe dyspnea gradually improved after a month, but at the time of admission she was still aware of difficulty in drawing her breath and had a loose cough productive of white phlegm, sometimes with lumps of greenish matter in it but never blood. Food occasionally caught in the throat, and at such times the patient had a sense of fullness under the mid-sternum.

The past history and review of the systems were essentially noncontributory.

Physical examination disclosed a well developed, well nourished woman who had evident respiratory distress with prolonged inspiration. She was not particularly hoarse. The thyroid gland was felt to be two and a half to three times enlarged but was symmetrical, soft, smooth and nontender. No

nodules were felt. Laryngoscopic examination revealed swollen mucous membranes of the vocal cords without impairment of function or tumor, and the tracheal mucosa below the larynx was reddened and edematous, with narrowing of the lumen apparently by extrinsic pressure.

Examination of the blood revealed a red-cell count of 4,400,000, with a hemoglobin of 12.2 gm., and a white-cell count of 6800, with 46 per cent neutrophils, 40 per cent lymphocytes, 6 per cent monocytes and 8 per cent eosinophils. The total protein was 5.7 gm. per 100 cc., and the prothrombin time 17 seconds (control, 16 seconds).

X-ray films of the neck and chest showed marked narrowing of the trachea opposite the lower cervical and upper thoracic spine. There was a soft-tissue density adjacent to the upper thoracic spine on the left, which may have represented the subclavian vessels. No obvious retrosternal extension was seen. The lung fields were clear, and the heart was of normal size.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Jacob Lerman: I should like to see the x-ray films.

Dr. Stanley M. Wyman: The only films available are those of the chest, which show a definite area of narrowing in the upper trachea, at about the level of the sixth and seventh cervical and the first thoracic vertebras. This narrowing is rather symmetrical and smooth. The detail, however, is not adequate to make much more of a statement than that. The prominence of the vascular tree in the mediastinum is seen on the left and appears to represent a prominent left subclavian artery; on the right there is no unusual prominence. The chest itself appears essentially normal. One cannot outline a definite mass in the lower part of the neck.

Dr. Lerman: Is there anyone here who can verify the description of the thyroid gland? Was it soft, smooth and symmetrical?

Dr. Moses H. Lurie: Yes. A barium swallow was done at the Eye and Ear Infirmary, and there was no evidence of outcropping.

Dr. Lerman: I found on reading the protocol that I was thinking in terms of aneurysm of the aorta or of the great vessels. After seeing the x-ray films I am obliged to discard this diagnosis completely.

The obvious place to look for trouble is the thyroid gland, although I am almost convinced that that was not the source of symptoms. I shall merely mention the various possible types of thyroid tumors that may produce such symptoms, particularly when such a gland encircles the trachea. A smooth goiter, a colloid goiter, with or without nodules, may encircle the trachea and produce compression with difficulty in breathing and the portion of the thyroid gland lying between the trachea and esophagus may also produce difficulty in swallowing. The more common type of thyroid tumor that does this is the result of chronic thyroiditis, either the Hashimoto or the Riedel type. However, from the description one has to exclude thyroiditis, which is a hard mass and often irregular. Similarly the description does not fit thyroid cancer, which is also a common cause for compression of the trachea. Either adenocarcinoma or papillary adenocarcinoma may produce compression by encircling the trachea. Either would produce a very hard, irregular tumor with evidence of tumor elsewhere in the neck or distally. In spite of the fact that the protocol emphasizes the importance of the thyroid swelling, I am forced to discard it as a source of symptoms.

What are the other possibilities? Anomalous vessels should be mentioned. There is not much evidence by x-ray examination or from the history, but anomaly of a large vessel could compress the trachea. However, such a condition would be discovered early in life. Benign mediastinal tumors, particularly benign cysts, most commonly dermoid cyst or teratoma, may produce compression of the trachea. More likely, because of the extensive involvement, a malignant mediastinal tumor has to be considered, such as lymphoma, sarcoma and so forth. I am afraid I cannot narrow it down further than this. I believe that the clinical and the x-ray evidence caused the surgeons to go after the thyroid gland as the cause of compression, but I am forced to conclude that there was a tumor in the upper mediastinum.

I should mention esophageal tumors, although the esophagus did not seem to play too large a role. Diverticulum of the esophagus producing compression of the trachea is a possibility. Also carcinoma of the esophagus is possible but unlikely.

I am obliged to leave the diagnosis as a malignant tumor of the upper mediastinum.

DR. BENJAMIN CASTLEMAN: Does anyone want to come a little closer to the diagnosis?

DR. ALFRED KRANES: The patient had an enlarged thyroid gland and pressure symptoms. I do not understand why Dr. Lerman discounted the thyroid gland so readily. Did he do so simply because the gland was soft?

DR. LERMAN: It was soft, smooth, nontender and without any nodules whatever.

DR. KRANES: Would you agree that it was soft, Dr. Lurie?

DR. LURIE: It was soft.

DR. OLIVER COPE: It takes considerable pressure to close the trachea off. The thyroid gland does it under two circumstances: in goiters that are fibrous, hard and invasive, as in either thyroiditis or carcinoma; and when the goiter is low enough to get caught in the upper thoracic strait. Dr. Lerman is justified in eliminating the thyroid gland — either the goiter was not the cause or the description of it was wrong.

DR. KRANES: I had assumed that the description was wrong.

DR. COPE: Malignant lesions in the trachea and esophagus invading the underneath capsule of the thyroid gland should be mentioned. We have had rare cases of that type. We had a case in which the disease apparently arose as a sarcoma of the trachea and invaded the thyroid gland and gave rise to this type of compression. We had 2 cases that I can remember from the esophagus. In both the esophageal cases the primary lesion was overlooked, and a diagnosis of carcinoma of the thyroid gland made. It was not until operation that the primary etiology was disclosed. Dr. Lerman is right in thinking of a malignant tumor elsewhere than the thyroid gland, and the upper mediastinum is a good location except that in this case we do not see it in the x-ray films.

DR. LERMAN: By the same reasoning, there is no x-ray evidence to point to the esophagus or trachea, and such diagnoses would be pure guesswork.

DR. COPE: In the 2 cases that I mentioned the invading lesion was small and overlooked in the x-ray films.

DR. EDWARD B. BENEDICT: We had a case of a papillary tumor of the thyroid gland that invaded the trachea and produced symptoms of dyspnea, hemoptysis and wheeze, which on bronchoscopy turned out to be a primary epidermoid carcinoma of the trachea.

DR. LURIE: When I first saw this woman my impression was that the lesion was entirely intralaryngeal. She had difficulty in inspiration and expiration but was able to do her work. When I looked at the larynx I was amazed to see that it had a fair airway, and the vocal cords anteriorly seemed to be lying in a reddened mass of mucous membrane that had bulged upward. With the larynx in complete abduction, a semi-doughnut projection of the trachea itself was seen. That made me think of rhinoscleroma, a very rare lesion— we have seen 4 or 5 cases in the Eye and Ear Infirmary. As I looked at this I debated a good deal whether I was justified in going in and trying to remove a piece of this mucous membrane through the larynx so that we could make a diagnosis. If we did that, I would have had to do a tracheotomy. If I did not succeed in getting a specimen, we were no better off than before. Having decided that, I began to wonder whether there was an extrinsic cause, and my first guess was the thyroid gland, especially a growth of the superior pole invading the larynx. I remember a case about twenty-five years ago in which I missed the diagnosis completely in trying to remove the tissue through the larynx and the patient died a year later from cancer of the thyroid gland. I finally asked Dr. Richard H. Sweet to explore externally, and a thyroidectomy was done.

CLINICAL DIAGNOSIS

Carcinoma of thyroid gland, with invasion of trachea.

DR. LERMAN'S DIAGNOSIS

Malignant tumor of upper mediastinum, with compression of trachea.

ANATOMICAL DIAGNOSIS

Adenoma of trachea, with extension into thyroid gland.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: I was present at this operation. The thyroid gland was symmetrical and slightly enlarged and on section was not remarkable. On

its posterior aspect was grayish tissue that looked like connective tissue. It was hard and fibrous and did not look at all granular as it would have been with carcinoma. I did a frozen section on a piece of it and found a tumor made up of uniform round cells and obviously epithelial. It reminded me of the adenomas that one sees in the bronchus. Dr. Sweet then found that the surface of the trachea was involved with this same tumor.

DR. LURIE: I then did a tracheotomy and looked into the mucous membrane of the trachea underneath the surface of the larynx and found that it was edematous, but there were no outcroppings and nothing that suggested a tumor mass.

DR. CASTLEMAN: Dr. Sweet took a biopsy of the trachea, and our final microscopical sections confirmed the diagnosis of adenoma. The cells were arranged in small glands corresponding to what is often called the mixed-tumor type of adenoma rather than the more common carcinoid type. By the mixed-tumor type I mean the type that is similar to the mixed-tumor of salivary-gland origin; it also resembles the cylindroma or epithelioma adenoides cysticum variety of the basal-cell epithelioma. This could be called a low-grade adenocarcinoma because it has invaded and infiltrated the posterior portion of the thyroid gland. I think we can say that the patient had had the tumor since the first symptoms began, sixteen years previously. It was very slowly growing and acted as any adenoma of the bronchus. There is still plenty of tumor left in the tracheal wall. We see adenomas of the bronchus with more tumor extrinsically than intrinsically, and it is not surprising that there was little intrinsic tumor in the trachea here. The problem arises regarding what should be done — whether a total laryngectomy should be performed or whether one should continue to follow her, knowing that the tumor is slowly growing but may metastasize to a regional lymph node and cause further difficulty by mediastinal spread.

This is the second case of tracheal adenoma that we have had here. The other was also of the same type and one that we diagnosed as epithelioma adenoides cysticum. It was in a man of sixty-eight who had had a local removal of the tumor two years previously, after having had symptoms for six months. Recently he developed a recurrence with symptoms of marked dyspnea, wheeze and hemoptysis. Dr. Sweet was able to resect a portion of the trachea, including a pedunculated tumor, 2 cm. long, attached on a 6 mm. base.

DR. JOHN STANBURY: If she had a total thyroidectomy, what was the consistence of the thyroid gland?

DR. CASTLEMAN: It was perfectly soft. The entire gland was removed. The only place it was not soft was on the posterior aspect, which was involved with tumor.

DR. BENEDICT: I might mention that in looking up the literature, I found 507 cases of primary carcinoma and 19 adenomas of the trachea. We have had 30 adenomas of the bronchus all of which were in the major bronchi. I just asked Dr. Lurie why he did not do a bronchoscopy and he said that he could not.

DR. LURIE: We could have, but we would have had to do a tracheotomy right away. I thought from the way the patient acted and from the x-ray studies that the lesion was better handled by an external rather than an internal approach. To get some of this specimen I would have had to go through the entire thickness of the mucous membrane of the larynx and trachea.

DR. BENEDICT: And there was no adenoma in the trachea?

DR. LURIE: Nothing that I could demonstrate. She now has a tracheotomy tube, and the swelling in the larynx and trachea is gradually going down. The breathing space is better than it was before operation.

DR. CASTLEMAN: Have you anything to add, Dr. Schall?

DR. LEROY A. SCHALL: This case has been covered so thoroughly that I do not believe I have anything to contribute. I saw the patient before operation and ruled against a bronchoscopy because of the swollen mucous membrane. I also thought that it was a surgical case and should be approached externally.

DR. LURIE: Why do you think that a laryngectomy would cure the case? Was there infiltration in the esophageal wall?

DR. CASTLEMAN: It is possible that there was invasion of the esophagus. I do not believe it was determined at operation.

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THE THORNDIKE AND ITS CASTLE

Some twenty-five years ago the Thorndike Memorial Laboratory of the Boston City Hospital was formally opened by His Honor James Michael Curley. This laboratory, dedicated to clinical research, was made possible through the generosity of George L. Thorndike (born in Salem in 1847), an alderman of the City of Boston. It has continued to function through the years — for the public good, let it be remembered — owing partly to the foresight and good will of Mr. Curley and partly to the wisdom of its successive directors — Francis W. Peabody, George R. Minot and William B. Castle.

In a very literal sense this laboratory existed and functioned two years before its public dedication in 1924, though much of the actual investigative work was carried on elsewhere, for the building was not then completed. One member of the staff worked in the private laboratory of Otto Folin (somehow he was neither Doctor nor Professor but simply and respectfully Otto Folin), who kept his notes on the backs of old envelopes and lectured in a superbly simple style.

Now there is more to this hospitality of Otto Folin than meets the eye. Then, as now, there was a close and cordial relation between the Thorndike and the Harvard Medical School. It was intended to be a co-operative enterprise and indeed it was. From the very start Francis Peabody made it clear to his staff — there were but four — that as their statures grew and as their interests changed there were open to the Thorndike men several channels of endeavor — the School, the Wards and the Laboratory. Yet the beginning and the end, the alpha and omega, were the same — the welfare of the patient. Francis Peabody wrote not long before his death: "What we need is less of the system and law that kills and more of the spirit that gives life." That spirit has always prevailed.

Basic research has its place. Without it progress would stand still; but beyond any question there must also be clinical investigation. And for clinical investigation there must be patients. For each there must be money. From the City of Boston come the patients; through the far-sighted generosity of the city officials comes, in large measure, the money and thus also comes the opportunity to investigate, and so to help, our fellow men.

Yet with all these golden opportunities the work of the Thorndike, now internationally known, would come to naught were there not wise and sympathetic medical guidance. There are problems of administration, problems of personnel and, of course, the decision as to what research shall be done by whom and in what manner. Such things require time, tact, knowledge, wisdom and considerable self-sacrifice.

The Thorndike has been especially fortunate in its directors. Each has had his own individuality and peculiarities.

The first, Francis Weld Peabody, brave soul that he was, needs praise from no man. With a subtle

force he launched the Thorndike on its course and early in its career laid down the major principle that the Laboratory, the Wards and the School were to be dedicated to one end — the education of the physician and the material benefit of the patient.

After Dr. Peabody's tragic and untimely death the directorship passed to his good friend, George Richards Minot, who was awarded the Nobel Prize not so very long after another good friend had said: "Poor George, still stuffing his patients full of liver when you and I know it's quite useless." Dr. Minot is a man of very varied interests. Being a horticulturist and botanist, he is justly proud of his garden and especially of his magnificent irises. He is a prolific writer of letters and there flows from his office a veritable flood of major and minor missives to friends and acquaintances all over the world. The only thing he dislikes is inactivity either in himself or in others. If Dr. Peabody's motto was: "*Do something useful*," Dr. Minot's is: "*Do something*." Those who have the good fortune to know him will recognize that in his heart of hearts he is a very kindly and a very thoughtful man. It is common knowledge that in spite of serious personal illness and in the face of many disappointments he had the faith, persistence and patience to further his own clinical investigation with patients on the wards and thus to initiate and perfect the therapy of Addisonian anemia. Dr. Minot merits and surely will receive a cordial welcome whenever he chooses to revisit the Thorndike, whose destiny he guided for over twenty years.

And now on Dr. Minot's retirement there comes a new director, William Bosworth Castle, Professor of Medicine, Master of Science (hon.), as rugged an individualist as ever trod the floors of that mecca of individualists — the Thorndike Memorial Laboratory, Boston City Hospital. Yet new is hardly an apt word; for twenty-three years ago, when the Thorndike was still in its childhood, Big Bill was resident physician pursuing there the type of research that he is now directing.

Trained as a physiologist he thinks in terms of physiology and thinks with almost frightening clarity. Dr. Castle's second outstanding quality — unswerving integrity and honesty not only with others but also with himself — is scarcely less impressive than the first. The world knows him as a great investigator, but the men on "Two" and "Four" — the Second and Fourth Medical Services — know that, to boot, he is a very shrewd clinician. What is more important, he is a truly great and very unassuming man.

This, then, is the new director of the Thorndike Memorial Laboratory, and director of the Second and Fourth Medical Services of the Boston City Hospital. Under his guidance and with the continued help of the powers-that-be the Thorndike will continue to flourish and through clinical investigation the public will continue to be adequately served. This is as it should be.

THE VAGINAL SMEAR AS A SCREENING TEST

Discussions of the periodic examination of apparently healthy people usually generate more heat than light. Before there will be real enthusiasm for applying a technic to broad segments of the population much more investigation is needed to determine the really essential elements of such examinations. We must know which procedures will be economically justified by the proportion of positive results when applied to large populations of varying sex, age and economic status.

The vaginal smear has been acclaimed in both the medical and the popular press as a most valuable adjunct in the diagnosis of uterine cancer. Since cervical cancer discovered early is often amenable to treatment, it is extremely important to evaluate this test and to determine its proper place in the definitive periodic examination that may be evolving.

Elsewhere in this issue of the *Journal* Lombard et al. report promising preliminary results from a large series of vaginal smears made on patients in the Massachusetts cancer hospitals and state-aided cancer clinics. Final evaluation awaits further follow-up study. These investigators point out certain inaccuracies and drawbacks of the technic sufficient to suggest hesitation in accepting it as a routine measure applicable to the entire female

population of cancer-bearing age at present. Studies elsewhere have given similar results, though some are more enthusiastic than others.

There is need for further investigation to indicate best methods of obtaining specimens, selection of cases for the test, proportion of error that must be expected, cost of the examination and the most suitable administrative procedures. This type of report shows critical judgment and full appreciation of the really broad significance of screening tests for the detection of incipient disease among the general population.

EFFECTS OF RUBELLA DURING PREGNANCY

LAST year Wesselhoeft[1] presented a very thorough review and discussion of the problems resulting from infection with German measles during pregnancy on the course of pregnancy and on the offspring. Aycock and Ingalls[2] also recently reviewed the subject of rubella, with particular reference to the problem of maternal disease as a principle in the epidemiology of congenital anomalies. At a recent meeting of the Midwestern Section of the American Federation for Clinical Research, Abel and Van Dellen[3] presented the results of their own survey of the effects of German measles during pregnancy. Their findings in 84 offspring of 82 mothers corroborated those of many authors quoted in the reviews mentioned above:

> Three stillbirths were recorded from mothers having German measles during the first trimester of pregnancy. Twenty-five of the children were normal at birth. In seven of these the mother contracted the disease during the first trimester, eleven during the second and seven in the last. Fifty-six of the infants were abnormal at birth, thirty-six with a single defect and twenty with more than one defect. In forty-four (76 per cent) of these, the mother told of having German measles during the first trimester of pregnancy, eight in the second, one in the third and unknown in three. Nineteen of the infants had congenital heart disease, seventeen had cataracts, fourteen were deaf, and seven were mentally deficient. Gastrointestinal, eye, spinal and skeletal abnormalities also occurred in lesser numbers.
>
> The most serious defects or combination of defects occur in women having German measles during the first trimester; defects are less serious and more infrequent in the second . . . in all, 87 per cent of the babies born of mothers having German measles during the first trimester were abnormal. No abnormalities developed in the third trimester.

Of particular interest is the manner in which these data were accumulated. One of the authors is a regular contributor to one of the popular syndicated health columns, which undoubtedly reaches millions of newspaper readers daily. This column was used as a medium for obtaining the information presented. He included a request for letters from mothers who had had German measles during pregnancy. They were asked to state the exact month of gestation in which the illness occurred and the effect on the offspring. Over 90 replies were thus obtained, and of these 82 were considered acceptable. The series includes two sets of twins, making a total of 84 children.

This method in reputable and critical hands undoubtedly opens up considerable possibilities for epidemiologic studies. The errors involved, however, are likely to be enormously greater than those obtained in studies of hospital histories or those based on personal surveys and interviews. It does, nevertheless, look like a very fertile field for obtaining at least a first approximation in many types of epidemiologic surveys.

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PLANNED PARENTHOOD REFERENDUM

FINAL petitions asking that the planned-parenthood question be placed on the November ballots in Massachusetts have been filed with the secretary of state of the Commonwealth. The 8429 signatures to these petitions, added to those obtained in 1947, make a total of 88,659. Numbered among the supporters of the thesis that physicians should be permitted to give contraceptive aid to married women for the protection of life or health, the Planned Parenthood League of Massachusetts claims 3363 Massachusetts physicians, or a majority of the resident members of the Massachusetts Medical Society.

In 1947 a bill providing for legalization of the contraceptive measure was initiated on a petition of 80,230 voters. After hearings before the Public Health Committee, this bill failed to pass either house.

Forty-six states of the Union now permit contraceptive advice to be given by physicians to married women for the protection of life or health.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CAPELES — Thomas F. Capeles, M.D., of Haverhill, died on August 12. He was in his sixty-fourth year.

Dr. Capeles received his degree from Tufts College Medical School in 1909. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

A brother survives.

CARROLL — Henry G. Carroll, M.D., of Salem, died on August 11. He was in his sixty-fifth year.

Dr. Carroll received his degree from Dartmouth Medical School in 1907. He was a member of the New England Ophthalmological Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, two sons, a daughter and a sister survive.

GRAINGER — Edward J. Grainger, M.D., of Winthrop, died on July 25. He was in his seventy-first year.

Dr. Grainger received his degree from Harvard Medical School in 1903. He was formerly vice-president on the staff of the Winthrop Community Hospital.

His widow, two brothers and a half-sister survive.

MARSH — Arthur W. Marsh, M.D., of Worcester, died June 24. He was in his eighty-second year.

Dr. Marsh received his degree from Harvard Medical School in 1895. He was a former president of Worcester District Medical Society, a member of the New England Surgical Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, two daughters, a brother and four grandchildren survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

ELKAVICH — Frank D. Elkavich, M.D., of Troy, died on July 27. He was in his fortieth year.

Dr. Elkavich received his degree from McGill University Faculty of Medicine in 1937. He was an associate staff member of the Elliot Community Hospital in Keene and a former president of the Cheshire County Medical Society. He was a fellow of the American Medical Association.

His widow, a son, a daughter, his parents, a brother and two sisters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

WOOD-TICK STUDY

The Massachusetts Department of Public Health is making a study of the wood-tick problem in the Commonwealth during the present season. This study was authorized by Chapter 36 of the Resolves of 1948.

The prevalence of ticks was rapidly declining by July 1, when the funds became available. Therefore, the most important part of the study this year is a survey to determine their geographical distribution. Much of the information, which is being collected on a questionnaire, is being supplemented by the identification of the ticks sent in by interested persons and of those collected by the personnel employed on the project.

The Department is most interested in receiving information about the prevalence of ticks outside the counties of Barnstable, Plymouth, Bristol, Nantucket and Dukes.

The co-operation of physicians in filling out questionnaires will be greatly appreciated. All information and any specimens collected should be forwarded to the Division of Communicable Diseases, 8 Beacon Street, Boston 8.

MISCELLANY

ALVARENGA PRIZE

In recognition of his studies on sludged blood the College of Physicians of Philadelphia has awarded the Alvarenga Prize for this year to Melvin H. Knisely, M.D., of the University of Chicago.

The Alvarenga Prize was established by the will of Pedro Francisco da Costa Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the College of Physicians on each anniversary of the death of the testator, July 14, 1883.

BOOK REVIEWS

Gastritis. By Rudolf Schindler, M.D. 8°, cloth, 462 pp., with 96 plates. New York: Grune and Stratton, 1947. $10.00.

This is a painstaking and thorough study of an interesting disease by a pioneer worker who has had a vast experience in over twenty-five hundred cases in the last twenty-eight years, and who has worked hard to establish this difficult disease on a sound, anatomic and clinical basis.

The gross and microscopical pathology is given in great detail (seventy-four pages) as a basis for the disease and for correlation with symptoms. Gastritis is classified as acute and chronic, and chronic gastritis is divided into superficial, atrophic and hypertrophic and gastritis in other diseases (tumors, ulcers, postoperative). The causes of chronic gastritis are varied and often unknown. The author does not believe that alcohol plays an important part. Gastritis was found in about 40 per cent of the patients gastroscoped for gastric symptoms.

It is interesting to compare the visible changes in the gastric mucosa described by Wolf and Wolff in their fistula patient after emotional upsets with the changes in acute superficial gastritis, but Schindler does not believe that chronic gastritis is due primarily to mental events.

There is great divergence of opinion about the symptoms of gastritis and about the importance of the disease. Some authors consider it one of the most important clinical conditions, and others a symptomless and insignificant disease. The symptoms described — epigastric pain, loss of appetite, nausea, vomiting, weight loss, weakness, anemia and bleeding — seem general in type and not diagnostic. There is nothing characteristic about the ordinary physical examination, gastric analysis or x-ray picture in the author's opinion, and diagnosis is based solely on gastroscopy at present. There is real difficulty in correlating the symptoms with the picture seen at gastroscopy, and the author says, "for a long time to come the clinical picture of chronic gastritis will be subject to discussion and controversy."

For treatment the author's advice is to get rid of the cause if one can be found — infections, tobacco, vitamin deficiency, and so forth — and to give a bland diet such as that used for peptic ulcer, with hydrochloric acid or enzymes and perhaps liver extract in the atrophic form. The author takes a rather gloomy view of operations on the stomach for peptic ulcer and the frequency of postoperative gastritis and the difficulty of its treatment. The relation of gastritis to peptic ulcer, cancer and pernicious anemia is very fully described.

There are brief reports of 55 cases and nearly a hundred pages of photomicrographs. The color prints are clear and well chosen. The book is well written, illustrated and printed, is a valuable contribution to this subject and is highly recommended to the internist and gastroenterologist.

Textbook of Human Physiology. By William F. Hamilton, Ph.D. 8°, cloth, 504 pp., with 121 illustrations. Philadelphia: F. A. Davis Company, 1947. $6.00.

The author makes it clear that the content of this book has been restricted to the things that the average medical student can encompass in the short time he is in the department of physiology. With this aim in view, much of importance has been left out in the hope that the clinic and the hospital will teach physiologic facts that the formal physiology course lacks the time to deal with. The author succeeds rather well in presenting the general outline of mechanisms whose normal or abnormal functioning is to be the central theme in the future life of the physician. There can be little doubt that the thirty-two chapters constitute merely the framework of physiology and that medical students will need to have their attention drawn to the urgent need for collateral reading. It seems to the reviewer that this textbook is more adapted for the use of college students than for that of medical students; nevertheless, the book will serve a useful purpose in orientation in a course in human physiology.

Diseases of the Joints and Rheumatism. By Kenneth Stone, D.M. (Oxon.), M.R.C.P. 8°, cloth, 362 pp., with 58 illustrations. New York: Grune and Stratton, 1947. $6.50.

This book contains much useful information about joints and about arthritis, but it fails to live up to its ambitious title. The classification of arthritis varies somewhat from that commonly employed, but it is logical and simple. The chapter on the physiology of joints is good. The author has an interesting theory in relating fibrositis and similar conditions to vagotonia. In future editions it is hoped that he will make a more complete discussion of symptoms and treatment of articular disease. The book is a useful but somewhat incomplete guide for the treatment of arthritis and allied conditions.

Fatigue and Impairment in Man. By S. Howard Bartley, Ph.D., and Eloise Chute, M.A. With a foreword by A. C. Ivy, Ph.D., M.D. First edition. 8°, cloth, 429 pp. New York: McGraw-Hill Book Company, Incorporated, 1947. $5.50.

The authors of this book are to be congratulated on a clearly written, comprehensive account of fatigue and impairment in man. The thesis is developed that very little of the work that has been done on fatigue refers to the experience of feeling tired and that fatigue is necessarily a reaction of the total organism. It is pointed out that the earliest studies dealing with impairment, work output and overt behavior have thrown light on fatigue merely in revealing what it is not, and in such approaches to the problem, considerations of bodily sensations, attitudes and matters of motivation have been almost totally neglected. No clear-cut distinction between fatigue and impairment has ever been made and constantly maintained.

Impairment is seen as referring to the condition of tissue, which is directly discovered only by physiologic and biochemical analysis, whereas fatigue is seen as an expression of the organization of the whole organism, which can be described only in personalistic terms. It is pointed out that fatigue is not an entity specified in quantitative units. The plan of the book is dictated by the distinction between fatigue and impairment, and after a chapter devoted to a detailed discussion of the various views on fatigue electrophysiologic studies, anoxemia, lack of sugar, temperature extremes and water-salt lacks, metabolism, hours and conditions of work in industries, drug action, neuromuscular activity, sleep, mental fatigue, personal factors in work situation, visual performance, conflict and frustration and chronic fatigue are considered. Each chapter is accompanied by many references, and at the end of the book appears a valuable list of visual aids.

This book unquestionably represents a fundamental contribution to the important subject of fatigue and impairment in man.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Bergey's Manual of Determinative Bacteriology. By Robert S. Breed, New York State Experiment Station (Cornell University), Geneva, New York; E. G. D. Murray, McGill University, Montreal; and A. Parker Hitchens, University of Pennsylvania, Philadelphia. Sixth edition. 8°, cloth, 1529 pp. Baltimore: The Williams and Wilkins Company, 1948. $15.00.

This standard reference work, first published in 1923 and last revised in 1939, has been completely revised and reset in a double column format for the sixth edition. The type content has been increased about 20 per cent. The work is supervised by a new board of editors, with Robert S. Breed of the original board of chairmen, assisted by a group of sixty contributors. Some changes have been made in the outline classification. The number of species of fission fungi has been increased from 1335 in the previous edition to 1630 in the present edition. There is a new source and habitat index. Many new binominals have been included in the index of names of genera and species. The preliminary text comprises a historical survey of classifications of bacteria, how bacteria are named and identified and rules of nomenclature. The descriptions of bacteria are then presented by orders, suborders and families. The two indexes mentioned above conclude the text. The printing is well done with a good type on a good light paper. The weight of the book is not excessive for its size. The work is an essential reference book for all medical and public libraries, and for all bacteriologists.

Life: Its nature and origin. By Jerome Alexander. 8°, cloth, 291 pp. New York: Reinhold Publishing Corporation, 1948. $5.00.

This monograph has been written primarily for the general reader, and each topic is treated in as simple and elementary a manner as possible. The fundamental objective of the work is to show that life is dominated by catalysis. In order are discussed the origin and physical basis of life, the nature of living units, the catalytic mechanism whereby life exists, persists and proceeds, immunology, genetics, evolution and embryology. There are special chapters on some catalytic aspects of disease and drugs and on philosophy, the guide to mental health. Each chapter has a list of references mentioned in the text. Author and subject indexes conclude the book. The text is well written and arranged, and the book is well published in every way. The volume should be in all large medical and general libraries.

Occupational Medicine and Industrial Hygiene. By Rutherford T. Johnstone, M.D., consultant in industrial health, and lecturer at the University of California, Los Angeles. 8°, cloth, 604 pp., with 117 illustrations. St. Louis: The C. V. Mosby Company, 1948. $10.00.

This new work on occupational medicine has been divided into four parts. The first comprises general topics, including workmen's compensation, medicolegal aspects, functions of the industrial physician, teaching of industrial medicine, diagnosis and laboratory procedures in diagnosis. The second and third parts and a portion of the fourth discuss the substances used in industrial plants — the solvents, metal and dust — and their hygienic and pathologic aspects. There are special

chapters on tuberculosis and pneumonia in industry, the dermatoses, synthetics and special industrial processes. Industrial hygiene in general is dealt with in two chapters, and the final chapter concerns pre-employment examinations and placement. The appendixes list the chemicals in common trade-name products and organic solvents used for cleaning or degreasing. A good index concludes the volume. Pertinent references are appended to each chapter. The material is well organized, and the text well written. The publishing is excellent. The work is recommended for all medical and public-health libraries and to industrial physicians.

Pathological Histology. By Robertson F. Ogilvie, M.D., F.R.C.P. (Edin.), F.R.S.E., lecturer in pathology and assistant in forensic medicine, University of Edinburgh, senior pathologist, Royal Infirmary, Edinburgh, pathologist to the Leith and Deaconess Hospitals, Edinburgh, and examiner in pathology and forensic medicine for the triple qualification. With a foreword by A. Murray Drennan, M.D., F.R.C.P. (Edin.), F.R.S.E., professor of pathology, University of Edinburgh. Third edition. 8°, cloth, 459 pp., with 260 photomicrographs in color. Baltimore: The Williams and Wilkins Company, 1947. $10.00.

This third edition of an English textbook, first published in 1940, has been extensively rewritten, revised and amplified. Fifteen subjects and plates have been added. The volume is designed for the use of students and as a companion to a standard textbook on pathology. A good index concludes the volume. The text is well printed with a good type on good light paper, with the color plates as inserts, making the book not too heavy for its size. The color work is excellent. The printing was done in Great Britain, and the binding in the United States. The volume should prove valuable as a reference work in all medical libraries.

History of Medicine: A correlative text, arranged according to subjects. By Cecilia C. Mettler, Ed.B., A.M., Ph.D. Edited by Fred A. Mettler, A.M., M.D., Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University. 8°, cloth, 1215 pp. Philadelphia: Blakiston Company, 1947. $8.50.

Dr. Mettler, in this new book on the history of medicine, has divided her subject into large, well recognized medical specialties and further subdivided them into chronologic periods within the subjects. The subjects covered comprise anatomy and physiology, pharmacology, pathology and bacteriology, physical diagnosis, medicine, neurology and psychiatry, venereology, dermatology, pediatrics, surgery, obstetrics and gynecology, ophthalmology and otology, and rhinolaryngology. The period covered is from the time of primitive man to the nineteenth century. Such important subjects as dentistry, veterinary medicine and public health are omitted. The modern period is considered as the seventeenth to nineteenth centuries. The treatment by subjects deprives the scholar of the broad perspective of a period in all branches of medicine, but as this approach may be found in the histories of Baas, Garrison and others, the new style of Dr. Mettler provides a reference work of outstanding value. Throughout the text extensive quotations are given from fundamental writings of various authors. In the section under medicine, entitled "Background of Early American Medicine," foreign names predominate to such an extent that it is very difficult to get a picture of American medicine of the eighteenth century. At least the two earliest medical books printed in the United States in Boston in 1708 and 1720, the *English Physician* and the *Pharmacopeia* of Nicolas Culpeper should have been noted. The text is well written and well printed in two columns on a coated paper too heavy for this type of book. The printing of personal names in heavy type is to be commended as good practice. A long list of selected readings is appended to each chapter. The volume concludes with comprehensive indexes of authors and subjects. Valuable historical maps are printed on the lining papers of the binding. This is a bad practice, since such printings are liable to defacement and destruction. This work is recommended as a reference source to all medical and general libraries and to all physicians interested in the history of medicine.

Symposium on Medicolegal Problems: Under the co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association. Edited by Samuel A. Levinson, M.D., Ph.D., University of Illinois College of Medicine for The Committees of the Institute of Medicine and The Chicago Bar Association. 12°, cloth, 255 pp. Philadelphia: J. B. Lippincott Company, 1948. $5.00.

The papers in this small volume were read and discussed at joint meetings by fourteen legal and medical authorities (including Professor Alan R. Moritz, of the Harvard Medical School) held at Chicago in 1945. The program was arranged by representative committees of the Institute of Medicine of Chicago and the Chicago Bar Association. The meetings were attended by physicians, lawyers, social workers, hospital managers, industrial commissioners, theologians and interested lay people. The subjects selected for discussion were the medical witness in court and expert testimony; artificial insemination and its medicolegal implications; the practice of pathology and its medicolegal problems; operations to produce sterility; medicolegal implications; trauma and tumors in industrial medicine; and scientific tests in evidence, including blood-grouping tests in disputed-paternity cases and chemical tests for intoxication. A physician and a lawyer, specialists in their particular fields, discussed each topic, the physician presenting the current medical opinion, and the lawyer interpreting the law. The discussions participated in by the group and audience were long, pertinent and instructive. Dr. Hawkinson, speaking on the medical witness and expert testimony, reviewed the history of attempts to regulate testimony, including the state plans, in which was mentioned the Massachusetts Briggs Law and the Minnesota plan of supervising and regulating medical testimony in the Minnesota courts, a joint plan of the State Medical Association and the State Bar Association. On the question of artificial insemination, with its medical, legal, social and religious problems, it was brought out that the law at present is at variance with scientific advance and that there is no law covering the whole problem. In the discussion of the practice of pathology, the question of various privileges claimed by physicians and the physician-patient relation were presented medically and legally. Also, an interpretation of the laws governing the human dead body was given. The Municipal Court of the City of Chicago, as early as 1922, was interested seriously in the problem of eugenic sterilization. In the discussion on this subject it was pointed out that the legal proof should guide the physician although he is convinced that there is sufficient scientific evidence to justify this type of operation. The consensus of medical opinion is that a single trauma does not produce tumors. The courts have held that, since the cause of tumors is unknown, trauma may be one of the unknown factors leading to tumor formation. The burden of proof rests on the scientist. The objective of the symposium was to bring into the open questions confronting the medical and legal professions. The meetings were very successful and a second series was held in 1947; it is hoped to make the meetings an annual affair. The text is well written in a simple style. The volume is well published in every way. The seemingly high price for a small volume is justified by the probable anticipated limited distribution. The book is recommended for all medical and legal libraries and to all persons interested in medicolegal problems.

The Rh Factor in the Clinic and the Laboratory. Edited by Joseph M. Hill, M.D., and William Dameshek, M.D. 4°, cloth, 192 pp., with illustrations and tables. New York: Grune and Stratton, 1948. $4.25.

This monograph is the joint work of fifteen authorities in their particular fields. The first article is a survey of the significance of the Rh factor, and is followed by articles on the various aspects of the Rh factor in clinical medicine. The last article is a historical review of Mexican blood transfusion. The book is well published in every way and should be in all medical libraries.

Laboratory Technique in Biology and Medicine. By E. V. Cowdry, professor of anatomy, Washington University, and director of research, The Barnard Free Skin and Cancer Hospital, St. Louis. Second edition. 8°, cloth, 269 pp. Baltimore: The Williams and Wilkins Company, 1948. $4.00.

The first edition of this manual was published in 1943 under the title, *Microscopic Technique.* The second edition has been revised to include methods developed since 1943. The

material is arranged alphabetically by subjects and printed in two columns to conserve space and paper. The volume should prove valuable as a ready reference source for all medical libraries and physicians and technicians.

Modern Treatment of Peptic Ulcer. By Asher Winkelstein, M.D., associate physician for gastroenterology and physician in charge of the Gastro-Intestinal Clinic, The Mount Sinai Hospital, New York City, and assistant professor of clinical medicine (gastroenterology), Columbia University, College of Physicians and Surgeons. 8°, cloth, 201 pp. New York: Oxford University Press, 1948. $4.00.

This small work considers the various aspects of the treatment of peptic ulcer. Etiology, pathology and prophylaxis are discussed, and ten chapters are devoted to drip therapy. There are chapters on vagotomy, therapy with enterogastrone, urogastrone and the protein hyperalimentation therapy, followed by consideration of the psychosomatic aspects. A bibliography and index conclude the volume. The publishing is well done in every way. The book should prove of value to physicians interested in the subject.

Oxford Loose-Leaf Medicine. (Sixteen reprints from the Supplements.) 4°, paper. New York: Oxford University Press, 1947. Available only to subscribers to complete sets of *Oxford Loose-Leaf Medicine.*

In 1947 the *Oxford Loose-Leaf Medicine* was amplified by the publication of a large number of revisions of various articles that were issued. Sixteen of these articles have been reprinted as separate publications. This material is available only to subscribers to complete sets of the work. Notable among these reprints may be mentioned Bright's disease, by Henry A. Christian; headache, by Walter C. Alvarez; arterial hypertension, by David Ayman; and scarlet fever, by James D. Trask and Paul L. Boisvert. The publication is well done in the usual excellent style of the Oxford University Press.

Introduction to the History of Science. Vol. III. *Science and Learning in the Fourteenth Century.* By George Sarton, D.Sc., L.H.D., and LL.D., professor of the history of science, Harvard University, and associate in the history of science, Carnegie Institute of Washington. In two parts. 4°, cloth, 1018 pp. Baltimore: Published for the Carnegie Institute of Washington by Williams and Wilkins Company, 1947. $20.00.

Dr. Sarton in the third volume of his monumental work on the history of science, covers the period of the fourteenth century. In the earlier sections the literature and learning from the time of Homer through the thirteenth century were presented in three large volumes. These early volumes, published in 1927 and 1931 and long out of print, have recently been reprinted by a photographic process and are now available at reasonable prices. This volume, comprising 2155 pages, has been issued in two large volumes, dividing the century into two equal parts. In the preface by the author there are noted corrections to Volume I and addenda to Volumes I and II. The style of the work has been maintained as originally planned. The general chapters preceding each half century — a survey of science and intellectual progress, religious background, the translators, education and the philosophical and cultural background — are intended for consecutive reading. The special chapters on each field of knowledge are intended for reference purposes. The sections on medicine comprise one hundred and sixty-one pages. Appended to each author considered are references to his works by recognized authorities. A complete table of contents for the century precedes the text. An addenda of forty-two pages, made necessary by the long time required for printing, and a general bibliography of forty-one pages conclude the text. A comprehensive general index of names and subjects of 174 pages, and special Greek, Chinese and Japanese indexes conclude the volume. The publishing is well done in every way. Dr. Sarton has spent the best part of his life in producing this scholarly and outstanding reference work that is practically impossible to review textually without writing another book. The complete set should be in all libraries, public and private, general and special. It is recommended for all medical libraries. It is hoped that Dr. Sarton will be able to continue his studies through the fifteenth century where the literature is tremendous in quantity and will live to see them published as the crowning achievement of his life.

Clinical Laboratory Methods and Diagnosis: A textbook on laboratory procedures with their interpretation. By R. B. H. Gradwohl, M.D., D.Sc., F.R.S.T.M. & H. (London), director to the Gradwohl Laboratories and Gradwohl School of Laboratory Technic, pathologist to Christian Hospital, and director, Research Laboratory, St. Louis Metropolitan Police Department, St. Louis. Fourth edition. In three volumes. 4°, cloth. Vol. I, 1296 pp., 362 illustrations and 41 color plates. Vol. II, 1114 pp., 328 illustrations and 9 color plates. Vol. III, *Parasitology and Tropical Medicine.* By R. B. H. Gradwohl, and Dr. Pedro Kouri, director, Institute of Tropical Medicine, professor of parasitology and tropical medicine, vice-dean of the Faculty of Medicine, Havana University, and director of Laboratorios Kuba, Havana. 864 pp., 420 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1948. $40.00 for the set.

This authoritative reference set has been greatly expanded over the previous edition of 1943, and contains 55 per cent more text material and 51 per cent more illustrative material. The revisions and expansions are so numerous that they cannot be listed in detail. A chapter on electrocardiography has been added, and the section on parasitology has been expanded from 394 to 819 pages and made a separate volume on parasitology and tropical medicine. References to the literature are printed as footnotes in their proper places. Volumes I and II, on clinical methods and diagnosis, are paged consecutively, with a comprehensive index at the end of the second volume. Volume III is paged separately and has its own index. The material is well arranged, and the typography, paper, illustrations and color work are excellent. The work is exceptional and should be in all medical libraries as an essential reference source.

NOTICES

ANNOUNCEMENTS

Dr. W. Charles Inman, assistant commissioner, Massachusetts Department of Mental Health, has been appointed superintendent of the Grafton State Hospital, North Grafton, Massachusetts. He will assume the duties of that position on September 16.

Drs. Leland S. McKittrick, John B. McKittrick and Thomas S. Risley announce the removal of their offices to 1180 Beacon Street, Brookline.

Dr. William F. Ryan announces the opening of his office for the practice of ophthalmology at 520 Commonwealth Avenue, Boston.

RESIDENCIES IN PSYCHIATRY AND NEUROLOGY

The Veterans Administration has immediate openings for at least a hundred young doctors interested in taking residency training in psychiatry or neurology, or both, it was recently announced.

Veterans Administration hospitals offering these residencies are situated in almost every section of the country. All are under supervision of the deans' committees, mostly composed of members of university faculties of Class A medical schools.

Applicants for residency training in these fields must be citizens of the United States and graduates of a school of medicine approved by the Veterans Administration and the Council on Medical Education and Hospitals of the American Medical Association, and must have completed an internship acceptable to the Veterans Administration.

In general, these residencies cover a three-year program of specialty training, although one-year and two-year programs are also available at most of the hospitals.

Junior or first-year residents must have completed a satisfactory internship and must be considered ready for specialization. Intermediate or second-year residents must have

the qualifications of a junior resident in addition to the equivalent of one year's training in the specialty. Senior residents must have the qualifications of a junior resident in addition to two years' training in the specialty.

Interested doctors may obtain information and application forms regarding the residencies by writing to the chief medical director, Veterans Administration, Washington 25, D. C.

Residency selection and residency grades for the applicant are recommended by the dean's committee supervising the program at the Veterans Administration hospital in which the applicant desires to train.

VETERANS ADMINISTRATION RESIDENCY-TRAINING PROGRAM IN NEUROPSYCHIATRY

A limited number of openings are available for appointment to the residency-training program in neuropsychiatry of the Veterans Administration Department of Medicine and Surgery. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program, which may be from one to three years, is given at:

Cushing Veterans Administration Hospital, Framingham, Massachusetts

Bedford Veterans Administration Hospital, Bedford, Massachusetts

The Mental Hygiene Clinic of the Boston Regional Office, Veterans Administration, Boston, Massachusetts

West Roxbury Veterans Administration Hospital, West Roxbury, Massachusetts

White River Junction Veterans Administration Hospital, White River Junction, Vermont.

Emphasis in the entire program is on psychiatry, with dynamic orientation, and includes closed ward, open ward, outpatient, child psychiatry and neurology.

Further information may be obtained from the chief neuropsychiatrist, Veterans Administration, Branch Office No. 1, 55 Tremont Street, Boston 8, Massachusetts.

JOHN AND MARY MARKLE FOUNDATION GRANTS

Medical schools in the United States and Canada are invited by the John and Mary R. Markle Foundation to make nominations for the second group of scholars in medical science on or before December 1, 1948. Each school, through the dean, may nominate one candidate. No nominations from individuals will be considered.

The program is designed to aid promising young men and women, planning careers in academic medicine, who have not yet made their reputations. They should have completed the usual fellowship training in some area of science related to medicine and should hold, or expect to hold, in the academic year 1949–1950 a full-time faculty appointment on the staff of a medical school.

Grants of $25,000, payable at the rate of $5,000 annually, will be made to the schools over a five-year period for the support of each scholar finally selected or his research, or both.

The number of scholars to be appointed in 1949 has not yet been determined. Sixteen were chosen in 1948. A new booklet describing the plan is available on request from the Foundation, 14 Wall Street, New York 5, New York.

INTERNSHIPS IN VETERANS ADMINISTRATION HOSPITALS

A limited number of internships in Veterans Administration hospitals will be offered qualified medical graduates. The internships will be limited to the seventy-five Veterans Administration hospitals now offering residency-training programs in co-operation with fifty-nine Class "A" medical schools over the country. They will be further limited to hospitals that have bachelor quarters available on the station grounds. A survey is in progress to determine what housing is available.

The two types of internship that will be available are as follows: "straight," for surgery, general medicine and other "straight" subjects; and "rotating," in which interns study, under a rotating schedule, surgery, general medicine and related subjects. Arrangements will be made for affiliated training for obstetrics and pediatrics in other than Veterans Administration hospitals. Such affiliated training may not involve more than 20 per cent of a year. The hospital at which the affiliated training is obtained must be approved for internship by the Council on Medical Education and Hospitals of the American Medical Association.

"Mixed" internships will not be offered.

Internships will be for one year, subject to reappointment for one year, if the reappointment is desired and recommended by the local dean's committee. The dean's committees, composed of members of university faculties or prominent local doctors, supervise the residency-training program and will also supervise internship training.

Annual pay for interns will not exceed $1,800 a year. Quarters, subsistence and laundry will be furnished. The stipend at each hospital will be determined by the Veterans Administration's chief medical director on recommendations of the deans' committees and in conformance with the existing scale of remuneration for interns in the locality.

Interns will be appointed in accordance with the national policy for all medical schools and hospitals, once each year on November 15, their tour of duty to begin the following July 1 or January 1 following July 1.

The new program is under the supervision of Dr. Paul B. Magnuson, chief medical director of the Veterans Administration, and Dr. Edward Harvey Cushing, assistant medical director for research and education in the Department of Medicine and Surgery, Veterans Administration. Those interested in residency training or internship should make application to the dean's committee at the university co-operating with Veterans Administration in the program, or to the manager of the hospital in the area in which they prefer to serve.

SILIFORM AMPOULES

Druggists and the medical profession are urged by the Food and Drug Administration, Federal Security Agency, to return all stocks of Siliform ampoules to the manufacturer, The Heilkraft Medical Company, Boston, Massachusetts. This injection drug, which should be sterile, is potentially dangerous since samples collected on the market contain living organisms. Siliform is injected by some physicians and osteopaths in the belief that it will relieve patients suffering with rheumatism as claimed by the manufacturer. The Food and Drug Administration found the contaminated samples after a routine inspection at the Heilkraft factory disclosed that the Siliform ampoules had been manufactured without sterilization. Intensive recall efforts by the manufacturer and the Food and Drug Administration since July 15 have not brought in all of the contaminated stocks. The article, which moves slowly, was shipped to 37 states from Maine to California and later was redistributed by wholesalers who cannot trace many of their sales. Some going back as far as 1946 have been found on the market. These ampoules may be in the hands of doctors, hospitals, clinics and retail and wholesale druggists.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, September 2

Friday, September 3

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Tuesday, September 7

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, September 8

*12:00 m.–1:00 p.m. Clinical Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

(*Notices concluded on page xi*)